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IT Anesthetics
Anti-infective agents
Antiarrhythmics
Antidepressants
Antiemetics
Antihistaminics
Antihypertensives
Antimalarials
Antitussives
Appetite depressants
Cardiotonics
Cholinergic agonists
Diuretics
Hypnotics and Sedatives
Inflammation inhibitors
Muscle relaxants
Neoplasm inhibitors
Nervous system stimulants
Sunscreens
Tranquilizers and Neuroleptics
Ulcer inhibitors
Vasoconstrictors
Vasodilators
Wound healing promoters
(topical compns. containing polyacrylamide and)

IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.13,7]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
RL: BIOL (Biological study)
(antimicrobial topical compns. containing polyacrylamide and)

L8 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:503333 CAPLUS
DOCUMENT NUMBER: 119:103333
TITLE: Enhanced skin penetration system for improved topical

09763499

delivery of drugs
INVENTOR(S): Deckner, George Endel; Lombardo, Brian Scott
PATENT ASSIGNEE(S): Richardson-Vicks, Inc., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

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PRIORITY APPLN. INFO.:

US 1991-778422	A	19911016
US 1992-948391	A	19920925
WO 1992-US8744	A	19921013
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
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CN 1072602	A	19930602	CN 1992-113328	19921016	<--
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IT Anesthetics
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Cardiotonics
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Hypnotics and Sedatives
Inflammation inhibitors
Muscle relaxants
Neoplasm inhibitors
Nervous system stimulants
Sunscreens
Tranquilizers and Neuroleptics
Ulcer inhibitors
Vasoconstrictors
Vasodilators
Wound healing promoters
(topical compns. containing dialkylaminoalkyl acrylate polymers and)

IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.13,7]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
RL: BIOL (Biological study)
(antimicrobial topical compns. containing dialkylaminoalkyl acrylate polymers and)

L8 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	1947:2215 CAPLUS
DOCUMENT NUMBER:	41:2215
ORIGINAL REFERENCE NO.:	41:414c-i,415a-i,416a-i
TITLE:	Aminoalkylphenols as antimalarials. I. Simply substituted α-aminocresols
AUTHOR(S):	Burckhalter, J. H.; Tendick, F. H.; Jones, Eldon M.; Holcomb, W. F.; Rawlins, A. L.
CORPORATE SOURCE:	Parke, Davis Co., Detroit, MI
SOURCE:	Journal of the American Chemical Society (1946), 68, 1894-1901 CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE:	Journal
LANGUAGE:	Unavailable

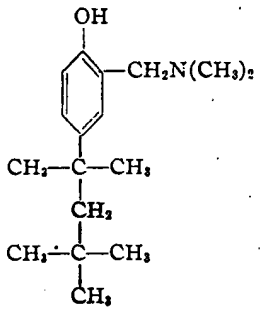
Jagoe

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS & COMPANY]

Aminoalkylphenols as Antimalarials. I. Simply Substituted α-Aminocresols[1]

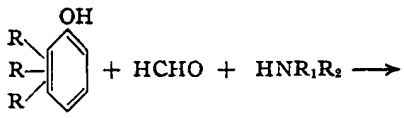
BY J. H. BURCKHALTER, F. H. TENDICK, ELDON M. JONES, W. F. HOLCOMB AND A. L. RAWLINS

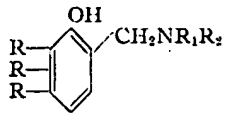
During an intensive program on antimalarials in this Laboratory, many types of compounds have been investigated in the search for a drug which might be a definite cure for malaria. One class of compounds which has appeared particularly promising is the substituted α-aminocresols. The first drug to be submitted for test in this series was α-dimethylamino-4-(1,1,3,3-tetramethylbutyl)-*o*-cresol.[1a]



Activity of Compound I 1 against trophozoite-induced chick malaria was established by Drs. R. J. Porter and L. T. Coggeshall, of the University of Michigan. This knowledge of antimalarial effectiveness by so unorthodox a compound indicated a lead which has resulted in the synthesis of several hundred compounds. More than one hundred of these constitute the subject of this first report.

Development of the first phase of this study has involved the testing of many compounds that are analogous or related to I 1.[1a] Several were obtained from an outside source,[2] but for the most part they were prepared in this Laboratory from various intermediate phenolic compounds by means of the Mannich reaction.[3,4] Phenols with at least one open position ortho or para to a phenolic hydroxyl were treated with formaldehyde and aliphatic amines to yield a wide variety of desired products. The following equation illustrates the general method used





R = hydrogen, alkyl, aryl, halo, alkoxy, aryloxy, etc.
R_1 = H or alkyl
R_2 = alkyl

As applied to phenolic compounds, the Mannich reaction may be carried out successfully with intermediates isolated from the treatment of formaldehyde with alkylamines. Dialkylaminomethanols,[5] dialkylamino alkyl ethers[6] and methylene-*bis*-dialkylamines[7] have all been employed in the preparation of α-dialkylamino-*o*-cresols. However, the authors generally chose simply to add the phenol to the mixture of dialkylamine, formaldehyde, and alcohol. Actually, this mixture has led to yields as great as were obtained from the use in a few experiments of pure dialkylaminomethyl alkyl ethers. Stock solutions containing four moles each of the dialkylamine and paraformaldehyde per liter of alcoholic solution have been kept for several months without apparent deterioration. For the sake of convenience in bringing together the reactants, the calculated volume of stock solution may simply be added to the phenol.

According to a recent report[8] no prior reference had been found in the literature to the interaction of a phenol with formaldehyde and diethylamine. Evidently, the claims of Bruson and his collaborators[9] had been overlooked. Because in this Laboratory diethylamine was found to enter into reaction so readily with formaldehyde and phenols, and especially because the diethylamino grouping is contained in several pharmaceutical agents, such as quinacrine, pamaquin, procaine, and trasentin, it was decided to employ this particular amine extensively in the outlined preparations.

Monoalkylamines have been used successfully with phenols in the Mannich reaction. With the exception of 2-aminoethanol,[10] a survey of the literature has failed to reveal any such previous use of primary aliphatic amines.

In general, paraformaldehyde and 37% formaldehyde have been found to be equally useful in this reaction.

The experiments of Décombe[11] afforded proof

(1) Presented at the 109th Meeting of the American Chemical Society, Atlantic City, N. J., April 8–12, 1946.

(1a) See Table I, Compound 1.

(2) Rohm and Haas Company, Philadelphia, Pa.

(3) Actually this reaction was applied to phenols [German Patent, *Frdl.*, **4**, 102 (1897)] several years before Mannich began his series of publications.

(4) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, chapter 10.

(5) German Patent 90,908; *Frdl.*, **4**, 103 (1897).

(6) (a) McLeod and Robinson, *J. Chem. Soc.*, **119**, 1470 (1921); (b) Harradence and Lions, *C. A.*, **33**, 7799 (1939); (c) Tseou and Yang, *J. Org. Chem.*, **4**, 123 (1939); (d) Mason and Zief, THIS JOURNAL, **62**, 1450 (1940).

(7) (a) German Patent 90,907; *Frdl.*, **4**, 102 (1897); (b) Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).

(8) Grillot and Gormley, THIS JOURNAL, **67**, 1968 (1945).

(9) U. S. Patents, 2,031,557, 2,033,092, 2,045,517 and 2,220,834.

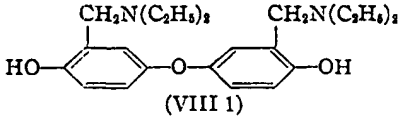
(10) U. S. Patent 2,114,122.

(11) Décombe, *Compt. rend.*, **196**, 866 (1933).

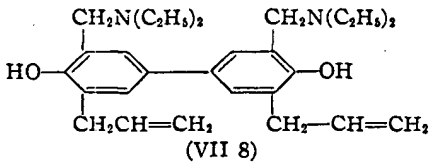
of nuclear substitution rather than ether formation by the entering aminomethyl group. The studies of others[12] determined whether or not the entry is ortho or para to the phenolic hydroxyl by catalytic hydrogenolysis of the α-aminocresols to the corresponding amino-free cresols, which were identified by comparison with structurally known cresols. In assigning structural formulas to the compounds in this paper, the data of Caldwell and Thompson[12a] have been advantageously used, with the assumption having been made that the identity of the starting amine exerts no influence upon the position taken by the entering group. Further, it was found that alkyl, phenyl or halo α-dialkylamino-*o*-cresols are insoluble in 5% caustic soda at room temperature, whereas the isomeric and analogous *p*-cresols are soluble. This observation has been valuable in confirming the structures of several compounds. Steric considerations, together with the fact that hydrogenolysis of 5-methyl-α-1-piperidyl-*o*-cresol yielded 2,5-dimethylphenol,[12a] were the guides in the tentative assignment of structural formulas to the following compounds: II 21, 23, 26, 33, 34; III 8, 28; VII 2. Only the analogy of quinolinols to naphthols[12a] determined the assignment of structures to VI 3, 4 and 5.[13]

The activity in avian malaria of certain (2,5-dimethyl-1-pyrryl)-quinolines has been known,[14] and so it was of interest to introduce the pyrryl grouping into the α-amino-*o*-cresol nucleus. The essential intermediate 4-(2,5-dimethyl-1-pyrryl)-phenol was prepared in good yield by treatment of *p*-aminophenol with acetonylacetone.

Intermediate 4,4′-oxybiphenol was obtained from diazotized 4,4′-diaminophenyl ether in 40% yield by improvement of an old procedure[15] and employed in the synthesis of VIII 1. Later, because of further interest in allyl compounds as a result of the activity of VII 8, the diallyl ether of 4,4′-oxybiphenol was rearranged to 3,3′-diallyl-4,4′-oxybiphenol. Application of a similar rearrangement produced the intermediate 2-allyl-4-*t*-butylphenol in satisfactory yield.

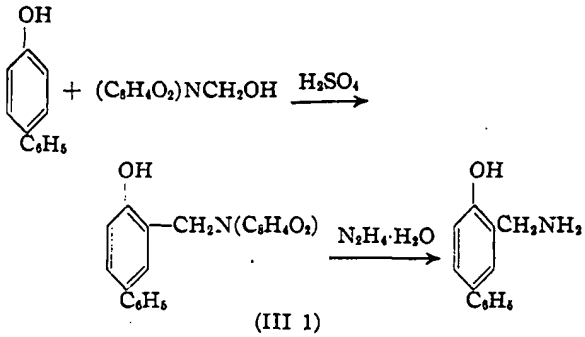


(VIII 1)



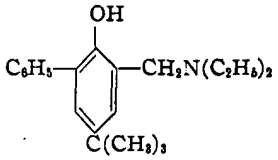
(VII 8)

In order to prepare a quantity of desired α-amino-4-phenyl-*o*-cresol (III 1), 4-phenylphenol was condensed with phthalimidomethanol and the resulting product hydrolyzed with hydrazine hydrate



(III 1)

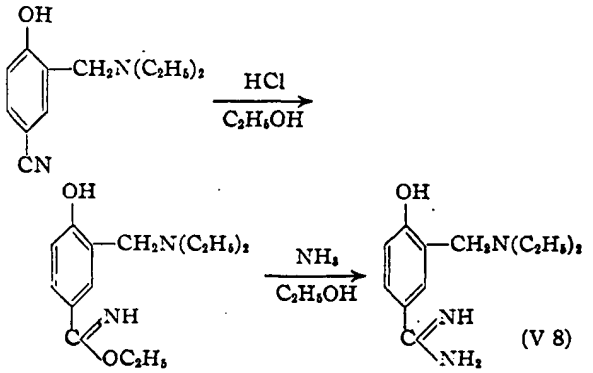
After the establishment of the interesting antimalarial activity of III 20, it was important to learn the effect of O-substitution on the activity



(III 20)

of this and certain related compounds. Three different O-acylated derivatives (III 21, VII 15 and 16) were prepared by heating the hydrochlorides of α-diethylamino-*o*-cresols with an excess of acyl anhydride. 2-Bromo-4-*t*-butyl-6-phenylanisole, which was obtained in good yield from the bromination of 4-*t*-butyl-6-phenylanisole, was converted by treatment of its Grignard reagent with diethylaminomethyl ethyl ether[6d] to O-methyl-4-*t*-butyl-6-phenyl-α-diethylamino-*o*-cresol (III 22).

The known effectiveness of amidines against human malaria[16] suggested a substitution of the guanyl radical in an α-amino-*o*-cresol nucleus. The synthesis was accomplished by conversion of 4-cyano-α-diethylamino-*o*-cresol (V 7) to the corresponding benziminoethyl ether. Treatment of the ether with alcoholic ammonia produced the desired 4-guanyl derivative (V 8).



(V 8)

(12) (a) Caldwell and Thompson, THIS JOURNAL, 61, 2354 (1939); (b) Cornforth, Cornforth and Robinson, *J. Chem. Soc.*, 168 (1943).

(13) Further reports on structure studies will appear in a later communication.

(14) Private communication. Chemical data: Gilman, Stuckwisch and Nobis, THIS JOURNAL, 68, 326 (1946).

(15) Haussermann and Bauer, *Ber.*, 30, 738 (1897).

(16) Glyn-Hughes, Lowrie and Yorke, *Ann. Trop. Med. Parasit.*, 32, 103 (1938).

Experimental

Procedure I.—An equimolecular mixture[17] of the appropriate amine and paraformaldehyde was warmed with sufficient alcohol to form a clear solution. This solution was cooled and added to an alcoholic solution or suspension of an equimolecular amount of the appropriate phenolic compound. The resulting mixture was usually allowed to stand for about an hour before it was heated at refluxing temperature for two hours. The volume of the mixture was reduced by evaporation or distillation, and the residue was extracted with ether. The ethereal extracts were washed, first with 5–10% sodium hydroxide solution and afterward with water, and finally dried over anhydrous potassium carbonate. (In certain cases solid free base was obtained by evaporation of the ether solution and recrystallized from the solvent given in the table). The hydrochloride was prepared by treating the dried ethereal solution with excess alcoholic hydrogen chloride. The solvent was ordinarily decanted from the precipitated salt which was triturated with fresh ether or other solvents until crystallization occurred.

Although in some experiments positive results appeared to depend upon the proper addition of the phenolic solution to the cooled amine—formaldehyde mixture, generally equally satisfactory results were effected by a simultaneous mixing of all the reactants.

Procedure II.—The preparative method followed for certain compounds was the same as Procedure I, except that the alkaline wash was eliminated. When aqueous formaldehyde was not used, the water wash and drying were omitted as well. Also, where a compound is listed in the tables as a free base, it was isolated from the reaction mixture as such without the ether extraction.

Procedure III.—An equimolecular mixture[17] of formaldehyde, appropriate amine and phenol in alcohol was refluxed for from two to four hours. The solution was diluted with water. The precipitated product was dissolved in ether and extracted with dilute hydrochloric acid. The acid extract was then separated, treated with an excess of ammonia and extracted with ether. The ethereal extract was washed with water, dried over potassium carbonate and evaporated to an oily residue, which was converted by means of concentrated hydrochloric acid or alcoholic hydrogen chloride to the hydrochloride.

Procedure IV.—The reaction was carried out as indicated in Procedure I, but the product was isolated by complete removal of the solvent and distillation of the free base under reduced pressure. To avoid polymerization, the pressure should usually not be greater than 10 mm. When desired, the hydrochloride was precipitated in the customary manner by treatment of an ethereal solution of the base with alcoholic hydrogen chloride.

Procedure V.—A mixture of equimolecular amounts of dimethylamine hydrochloride, paraformaldehyde and the suitable phenol in alcoholic solution was refluxed for two hours. The volatile materials were removed by distillation and the residue poured into several times its volume of ether. Successive triturations and decantations using fresh volumes of ether and acetone were carried out until a crystalline product formed.

Procedure VI.—The *bis*-(diethylamino)-bi-*o*-cresol dihydrochloride was dissolved in several times its weight of acetic or propionic anhydride and heated to 130°. Several drops of concentrated sulfuric acid were added and the solution cooled. The diester dihydrochloride was precipitated with ether.

4-(2,5-Dimethyl-1-pyrryl)-phenol.—A mixture of 57 g. (0.5 mole) of acetonylacetone, 54.5 g. (0.5 mole) of *p*-aminophenol, 100 cc. of absolute alcohol and 1 cc. of acetic acid was refluxed for twenty hours and then poured into 600 cc. of water. The oily precipitate solidified upon cooling; m. p. 90–95°. The crude product was dissolved in dilute potassium hydroxide solution and reprecipitated by passing in a stream of carbon dioxide; m. p. 102–104°. Reprecipitation from an alkaline solution with acetic acid did not change the melting point, but recrystallization from ligroin yielded 76.6 g. (82%) of a white product which melted at 104–106°. This intermediate was used as such without analysis for the preparation of V 5 because of its discoloration upon exposure to light and air.

4,4′-Oxybiphenol.—To a 12-liter flask containing a solution of 50 cc. of concentrated hydrochloric acid and 115 cc. of concentrated sulfuric acid in five liters of water at 40–50°, there was added 60 g. (0.3 mole) of 4,4′-diaminophenyl ether, and the mixture was stirred until a clear solution resulted (one to two hours). By application of ice externally and internally, the mixture was cooled to 0–5°, and then a solution of 41.4 g. of sodium nitrite in 100 cc. of water was added with stirring and cooling during a period of thirty minutes. After standing overnight the mixture was boiled until a sample gave no red color with alkaline β-naphthol (two to three hours). Considerable tar had formed, so the liquid was filtered hot through Supercel and poured into 12-liter flask containing 2 kg. of sodium chloride, which was dissolved with stirring. Then the solution was cooled to room temperature and the precipitated solid collected. The wet filter cake was dissolved in 300 cc. of ether and filtered through Supercel. Evaporation of the ether gave 25 g. of product; m. p. 154–158°. After dissolving this material in dilute potassium hydroxide and reprecipitating with dilute hydrochloric acid, 24 g. (40% yield) of 4,4′-oxybiphenol was obtained; m. p. 165–167°.[18] The product is slightly soluble in benzene and toluene, and is very soluble in ethanol, acetone and ether. It may be recrystallized from large volumes of water.

3,3′-Diallyl-4,4′-oxybiphenol.—A mixture of 20.2 g. (0.1 mole) of 4,4′-oxybiphenol, 27.8 g. (0.2 mole) of potassium carbonate and 150 cc. of acetone was heated under reflux and 24.2 g. (0.2 mole) of allyl bromide was added dropwise to the mixture during a period of thirty minutes. Refluxing was continued for two hours, after which water was added and the mixture was extracted with ether. The ethereal extract was washed first with dilute potassium hydroxide solution and then with water and finally dried over potassium carbonate. After removal of the ether by evaporation, a crystalline residue of 3,3′-diallyl-4,4′-oxybiphenol weighing 22 g. remained; m. p. 78–80°.

The crude allyl ether was placed in a 50-cc. Claisen flask and heated to 250° *in vacuo* (20 mm.). Then the liquid was distilled under reduced pressure. The product was a thick liquid which was collected at 195–200° (1.5 mm.); yield 16 g. (52%).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 76.57; H, 6.43. Found: C, 76.05; H, 6.51.

2-Allyl-4-*t*-butylphenol.—The foregoing general procedure was followed in this preparation. The rearrangement was carried out by refluxing the ether for five minutes after the temperature of the liquid had reached a maximum of 268°. Distillation *in vacuo* gave a colorless liquid which boiled at 127–129° (8 mm.). The over-all yield was 79%.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06: H. 9.53. Found: C, 82.06; H, 9.32.

4-Phenyl-α-amino-*o*-cresol (III 1).—A mixture of 17 g. (0.1 mole) of 4-phenylphenol, 18 g. (0.1 mole) of phthalimidomethanol,[19] 200 cc. of benzene and six drops of concentrated sulfuric acid was refluxed for two hours during which time the water was removed by means of a take-off attachment. The solution was then evaporated to dryness and the residue, dissolved in 100 cc. of alcohol, was heated to reflux with 10 cc. of 85% hydrazine hydrate solution. After twenty minutes, the mixture suddenly solidified. Two hundred cc. of 3 *N* hydrochloric acid was added and the mixture boiled for an hour. It was then cooled and filtered. Excess ammonia was added to the filtrate to pre-

(17) The molecular proportions of formaldehyde and amine to phenol used in these preparations depended upon the number of alkylaminomethyl groups desired in the final product. For example, two moles of both were used for each mole of intermediate biphenol in the preparation of VII 1.

(18) Haussermann and Bauer [*Ber.*, **30**, 738 (1897)] gave 160–161° and indicated a low yield.

(19) Sachs, *ibid.*, **31**, 3232 (1898).

TABLE I

4-(1,1,3,3-TETRAMETHYLBUTYL)-α-AMINO-*o*-CRESOLS

No.	SN	Q equiv. B4	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	5018	0.3[a]	α-Dimethylamino[b,c]										
2	7867	.03i	α-Dimethylamino[b,d]										
3	7494	.05i	α-Di-*n*-amylamino[e]	I	143[g]	81	$C_{23}H_{43}NO \cdot HBr$					3.07	3.09
4	6798	.02	α-1-Piperidyl[c]	II	70[h]	95							
5	7137	.03i	α-4-Morpholinyl	III	200[i]	52	$C_{15}H_{23}NO_3 \cdot HCl$	66.71	66.93	9.43	9.28		
6	7821	.08	α-Ethyl-2-hydroxyethylamino	II	151[j]	93	$C_{17}H_{29}NO_2 \cdot HCl$	66.35	66.49	9.97	9.92		
7	6803	.03	α-Di-2-hydroxyethylamino	II	81[k]	24	$C_{18}H_{33}NO_3$					4.32	4.31
8	6797	.02i	α-Dibenzylamino	II	118[h]	70	$C_{29}H_{37}NO$	83.80	83.94	8.98	8.64		
9	6804	.20	6-Methyl-α-dimethylamino[b]										
10	7491	.11	6-Chloro-α-diethylamino[b,f]										

[a] Q 0.67i by J1 test. [b] Sample from Rohm and Haas Co. [c] Described in U. S. Patent 2,033,092. [d] Methochloride. [e] Intermediate phenol from Rohm and Haas Co. [f] Phosphate. [g] From chloroform–ligroin. [h] From ethanol. [i] From iso-propanol. [j] From ethanol–acetone. [k] From ligroin.

TABLE II

ALKYL AND HALO α-AMINO-*o*-CRESOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
				α-Dimethylamino-								
1	7502	0.03i		None[b]								
2	7498	.03i	0.05i	6-Methyl[b]								
3	7497	.1		4-*t*-Butyl[b,c]								
				α-Diethylamino-								
4	4769		0.2i	None[d]	IV	135[u]	32	$C_{11}H_{17}NO \cdot HCl$	61.24	61.17	8.41	8.47
5	6802	.05t		6-Methyl[e]	IV	161[v]	36	$C_{12}H_{19}NO \cdot HCl$	62.73	63.01	8.78	8.34
6	6805	.04		4-Methyl[f]	IV		71	$C_{12}H_{19}NO$				
			0.05i		...	157[p]	..	$C_{12}H_{19}NO \cdot HCl$[n]	62.73	62.68	8.78	8.95
7	7496	.4		4-*t*-Butyl	III	36[w]	38	$C_{14}H_{23}NO$	76.54	76.55	10.71	10.20
8	7741	.07i		4-*t*-Butyl-6-hydroxy	II	142[w]	96	$C_{14}H_{23}NO_2$	71.67	71.88	10.03	9.80
9	7503	.18t		4-2′-Methylcyclohexyl[g]	I	148[x]	46	$C_{14}H_{29}NO \cdot HCl$	69.31	69.53	9.70	9.41
10	8459	.1		6-*n*-Heptyl[h,i]	II	126[v]	46	$C_{14}H_{23}NO_2 \cdot HCl$[o]	65.13	65.26	10.33	10.25
11	8458	.04i		4-*n*-Octyl[h,i]	II	86[v]	39	$C_{15}H_{25}NO \cdot HCl$	69.64	69.45	10.45	10.36
12	7500	.10		4-*n*-Dodecyl[b]								
13	7493	.06		4-Chloro	I	158[t]	56	$C_{11}H_{16}ClNO \cdot HCl$	52.78	52.93	6.85	6.89
14	7488	.06		4-Bromo[h]	II	165[aa]	..	$C_{11}H_{16}BrNO \cdot HCl$[p]				
15	7296	.05i		6-Bromo	I	175[bb]	10	$C_{11}H_{16}BrNO \cdot HCl$	44.82	45.08	5.82	5.68
16	13700	.05i		4-Methyl-6-bromo[h]	I	170[bb]	65	$C_{12}H_{18}BrNO \cdot HCl$	46.69	46.89	6.20	6.29
17	8456	.4t		4-Bromo-6-methyl[h]	I	175[cc]	38	$C_{12}H_{18}BrNO \cdot HCl$	46.69	46.66	6.20	6.45
18	9000	.06		4-Cyclohexyl-6-bromo[h]	II	92[w]	63	$C_{17}H_{26}BrNO$	60.00	60.21	7.69	7.58
19	8294		1.0	4-Chloro-6,1′-methallyl[h]	III	130[s]	44	$C_{15}H_{22}ClNO \cdot HCl$[q]				
20	7492	.1		4-*t*-Amyl-6-chloro[h]	I	148[dd]	83	$C_{16}H_{26}ClNO \cdot HCl$	59.99	60.23	8.50	8.50
21	8497	.08		4-Chloro-5-methyl	III	192[s]	51	$C_{12}H_{18}ClNO \cdot HCl$[r]				
22	8370	.06		3-Methyl-4-chloro-6-*n*-hexyl	II	132[v]	81	$C_{19}H_{32}ClNO_2 \cdot HCl$[o]	59.01	59.13	9.08	9.26
23	7304	.2t		4,5-Dimethyl	I	190[u]	83	$C_{12}H_{19}NO \cdot HCl$	64.05	64.16	9.10	9.10
24	10989	.25		3,5-Dimethyl	II	156[bb]	77	$C_{12}H_{19}NO \cdot HCl$	64.05	64.31	9.10	9.07
25	7303	.10	0.4t	3,5,6-Trimethyl[k]	I	175[u]	94	$C_{13}H_{21}NO \cdot HCl$	65.22	65.14	9.38	9.05
26	10505	.05i		4-*t*-Butyl-5-methyl[l]	I	177[w]	12	$C_{15}H_{25}NO \cdot HCl$	67.22	67.05	9.87	9.63
27	9576	.3	1.0	4-*t*-Butyl-6-methyl[h]	I	150[bb]	45	$C_{15}H_{25}NO \cdot HCl$	67.22	67.46	9.87	9.89
28	7819	.2		4-*t*-Butyl-6-allyl	III	139[v]	48	$C_{18}H_{29}NO \cdot HCl$[s]				
29	8051	.17		4-*t*-Amyl-6-allyl[h]	III	151[s]	41	$C_{19}H_{31}NO \cdot HCl$[t]				
30	8383	.18		4-Cyclohexyl-6-allyl[h]	II	142[w]	59	$C_{20}H_{31}NO \cdot HCl$	71.08	71.37	9.55	9.52
31	8393	2.0[a]		4-*t*-Butyl-6-cyclohexyl[h]	II	192[w]	56	$C_{21}H_{33}NO \cdot HCl$	71.26	71.58	10.25	10.00
32	6799	0.04i		4-Chloro-α-1-piperidyl[m]	II	57[w]	82	$C_{12}H_{16}ClNO$	63.85	63.94	7.15	7.10
33	7298	.08i		4-Chloro-5-methyl-α-1-piperidyl[j]	III	85[w]	62	$C_{13}H_{18}ClNO$	65.14	64.91	7.57	7.55
34	6796	.05i		4-Chloro-5-methyl-α-4-morpholinyl[j]	III	215[aa]	31	$C_{12}H_{16}ClNO_2 \cdot HCl$	51.80	52.00	6.16	5.81

[a] Q 1.0 by D1 tests. [b] Sample from Rohm and Haas Co. [c] Hydrochloride. [d] Base distilled at 100–110° (3 mm.). Grillot and Gormley [THIS JOURNAL, 67, 1968 (1945)] found 63–67° (1–2 mm.). [e] Base distilled at 107–108° (3 mm.). Grillot and Gormley [*ibid.*] found 93–97° (1–2 mm.). [f] B. p. ,122° (4 mm.). [g] Intermediate phenol from Monsanto Chemical Co., St. Louis. [h] Intermediate phenol from Dow Chemical Co. [i] Microanalysis by Arlington Laboratories. [j] Intermediate phenol from Monsanto Chemicals, Ltd. [k] Intermediate phenol from Shell Development Co. [l] Intermediate phenol from The Koppers Co. [m] Yang describes this compound prepared by essentially the same procedure (m. p. 55°) in *J. Org. Chem.*, 10, 67 (1945), but assigns the structure of 4-chloro-α-1-piperidyl-*m*-cresol. [n] Prepared by treatment of an ethereal solution of the base with alcoholic hydrochloric acid. [o] Includes $1H_2O$. [p] *Anal.* for N: Calcd. 4.75. Found 4.91. [q] *Anal.* for N: Calcd. 4.64. Found 4.70. [r] *Anal.* for N: Calcd. 5.30. Found 5.21. [s] *Anal.* for N: Calcd. 4.49. Found 4.57. [t] *Anal.* for N: Calcd. 4.30. Found 4.23. [u] From acetone–ethanol. [v] From acetone. [w] From ethanol. [x] From acetone–ethyl acetate. [y] From ethyl acetate. [z] From isopropanol–ether. [aa] From isopropanol. [bb] From ethanol–ether. [cc] From methanol–acetone. [dd] From acetone–ether.

TABLE III

ARYL α-AMINO-*o*-CRESOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	9578		1.0	4-Phenyl-α-amino[a]		235[b]		$C_{16}H_{15}ClNO.HCl$	66.24	65.88	5.97	5.90
2	5017	0.2	0.5	4-Phenyl-α-dimethylamino[b]								
		D1 0.12										
		D2 0.25										
3	7301	.12i		4-Phenyl-α-diethylamino	I	165[j]	46	$C_{17}H_{21}NO.HCl$	69.97	70.23	7.60	7.37
4	7487	.03i		4-Phenyl-α-ethyl-2-hydroxyethylamino	III	149[m]	18	$C_{17}H_{21}NO_2.HCl$	66.34	66.30	7.21	7.25
5	7142	.02		4-Phenyl-α-1-piperidyl	III	90[n]	62	$C_{18}H_{21}NO$	80.87	80.71	7.92	7.61
6	7143	.03i		4-Phenyl-α-4-morpholinyl	III	91[n]	50	$C_{17}H_{19}NO_2$	75.82	75.66	7.11	7.06
7	7740	.05i	0.2t	4-Phenyl-6-hydroxy-α-diethylamino	II	108[m]	64	$C_{17}H_{21}NO_2$	75.24	75.36	7.80	7.95
8	7820	.4	0.4t	5-Phenyl-α-diethylamino[c]	I	78[o]	76	$C_{17}H_{21}NO$	79.96	79.77	8.29	8.26
9	6895	.35	1.0	6-Phenyl-α-diethylamino[d]								
10	9283	.2		6-Phenyl-α-ethylamino[c]	I	186[j]	..	$C_{16}H_{17}NO.HCl$	68.30	68.38	6.88	6.87
11	8268	.1		6-Phenyl-α-2-hydroxyethylamino[e]								
		D1 0.06										
		D2 0.25										
12	8298	.13		6-Phenyl-α-*n*-decylamino[c]	I	134[p]	50[f]	$C_{23}H_{33}NO.HCl$	73.47	73.53	9.11	9.03
13			0.17	4-Phenyl-6-chloro-α-diethylamino[c]	I	141[p]	31	$C_{17}H_{20}ClN.OHCl$[g]	62.58	62.46	6.49	6.30
14	7489	.01i		4-Phenyl-6-chloro-α-1-piperidyl[c]	II	80[n]	92	$C_{18}H_{20}ClNO$	71.63	71.41	6.68	6.68
15	7294	.05i		4-Phenyl-6-bromo-α-diethylamino[c]	I	141[n]	89	$C_{17}H_{20}BrNO.HCl$	55.07	54.91	5.71	5.71
16	7297	.18	1.0	4-Chloro-6-phenyl-α-diethylamino	I	128[m]	43	$C_{17}H_{20}ClNO.HCl$	62.58	62.57	6.49	6.16
		D1 0.5										
		D2 1.0										
17	14111	.3		4-Bromo-6-phenyl-α-diethylamino[c]	I	146[m]	70	$C_{17}H_{20}BrNO.HCl$[h]				
18	7490	.2		2-Chloro-3-phenyl-α-diethylamino[c]	I	65[n]	54	$C_{17}H_{20}ClNO$[i]	70.45	70.20	6.96	6.84
19	7282	1.5	2.0	4-*t*-Butyl-6-phenyl-α-dimethylamino[c]	I	207[m]	85	$C_{19}H_{25}NO.HCl$	71.34	71.36	8.19	8.00
20	7744	2.0	1.0i	4-*t*-Butyl-6-phenyl-α-diethylamino[c]	I	173[p]	83	$C_{21}H_{29}NO.HCl$	72.50	72.54	8.69	8.71
		D1 2.0										
21	9636	1.5		O-Acetyl-4-*t*-butyl-6-phenyl-α-diethylamino[a]		201[q]	67	$C_{23}H_{31}NO_2.HCl$	70.84	70.92	8.27	8.23
22	10122	0.16t		O-Methyl-4-*t*-butyl-6-phenyl-α-diethylamino[a]		142[r]	50	$C_{21}H_{31}NO.HCl$	73.00	73.03	8.91	9.07
23	9557	2.5		4-*t*-Butyl-6-phenyl-α-ethylamino[c]	II	216[m]	42	$C_{19}H_{25}NO.HCl$	71.34	71.36	8.19	8.36
24	9202	1.0		4-*t*-Butyl-6-phenyl-α-2-hydroxyethylamino[c]	II	158[s]	45	$C_{19}H_{25}NO_4.HCl$[j]	61.36	61.70	8.10	7.82
25	8368	1.6	2.0	4-*t*-Amyl-6-phenyl-α-diethylamino[c]	II	168[p]	80	$C_{23}H_{31}NO.HCl$	73.00	72.94	8.91	8.70
		D1 1.0										
26	8303	0.6	0.2	4-(1,1,3,3-Tetramethylbutyl)-6-phenyl-α-diethylamino[c]	II	178[s]	88	$C_{25}H_{37}NO.HCl$	74.31	74.31	9.48	9.39
		D1 1.0										
27	8289	0.55		4-Phenyl-6-1-methallyl-α-diethylamino	I	151[q]	50	$C_{21}H_{27}NO.HCl$	72.91	72.92	8.16	8.39
28	8500	0.08		4-*t*-Butyl-5-phenyl-α-diethylamino[c]	II	190[p]	83	$C_{21}H_{29}NO.HCl$	72.50	72.22	8.69	8.66

[a] For Preparation see the Experimental Part. [b] Sample obtained from Rohm and Haas Company. [c] Intermediate phenol from Dow Chemical Company. [d] Preparation and proof of structure will appear in a later publication; tested as the hydrochloride. [e] Described in U. S. Patent 2,114,122. [f] By Procedure V the percentage yield was 47. [g] *Anal.* for N: Calcd. 4.29. Found 4.14. [h] *Anal.* for N: Calcd. 3.78. Found 3.72. [i] *Anal.* for N: Calcd. 4.83. Found 4.90. [j] Includes $2H_2O$. [k] From ethanol–ligroin. [l] From ethanol–acetone. [m] From isopropanol. [n] From ethanol. [o] From dilute ethanol. [p] From acetone. [q] From ethyl acetate. [r] From toluene. [s] From ethanol–ether.

cipitate 6 g. of solid base; m. p. 157–158°. The crude product was dissolved in potassium hydroxide solution and the mixture was filtered through Supercel. A stream of carbon dioxide through the solution reprecipitated 5.8 g. (29% yield) of light tan colored base; m. p. 157–158°.

The hydrochloride was prepared by dissolving the base in alcoholic hydrogen chloride. By evaporating the solution to a low volume, a yellow crystalline precipitate formed; m. p. 228–233°. After treatment with Norite in alcoholic solution and recrystallization twice from alcohol–ligroin, the white product melted at 235°.

O-Acetyl-4-*t*-butyl-6-phenyl-α-diethylamino-*o*-cresol (III 21).—A mixture of 20 g. (0.057 mole) of α-diethylamino-4-*t*-butyl-6-phenyl-*o*-cresol hydrochloride (III 20) and 70 g. of acetic anhydride was warmed until complete solution was effected. After a drop of concentrated sulfuric acid had been added, the solution was allowed to stand for about five minutes before the excess acetic anhydride was removed under reduced pressure. The crude crystalline hydrochloride was collected and washed with ether.

O-Methyl-4-*t*-butyl-6-phenyl-α-diethylamino-*o*-cresol (III 22).—From 144 g. (0.637 mole) of 4-*t*-butyl-*o*-phenylphenol, an essentially quantitative yield of 4-*t*-butyl-*o*-phenylanisole [b. p. 143–145 (3 mm.)] was obtained by methylation with dimethyl sulfate.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 85.06; H, 8.43.

To a stirred solution of 144 g. (0.6 mole) of 4-*t*-butyl-*o*-phenylanisole in 100 cc. of glacial acetic acid, 96 g. (0.6 mole) of bromine in 100 cc. of glacial acetic acid was added over a period of an hour. At the end of the addition, the temperature of the solution was 40°. After standing for half an hour, the solution was poured into two liters of water. The resulting mixture was extracted with ether and the ether layer washed with two different portions of water. After removal of the solvent, the residue was distilled at 154–160° (2 mm.) to yield 159 g. (83%) of product. Upon redistillation, 130 g. was collected at 147–148° (2 mm.), yielding 68% of an oil considered to be 2-bromo-4-*t*-butyl-6-phenylanisole.

A Grignard reagent was made from 76.3 g. (0.24 mole) of 2-bromo-4-*t*-butyl-6-phenylanisole, 5.8 g. of magnesium turnings and 250 cc. of dry ether. Initiation of the reaction was very difficult despite the use of customary pro-

TABLE IV

BENZYL-TYPE α-DIETHYLAMINO-*o*-CRESOLS

No.	SN	Q equiv. B4	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7499	0.13[a]	4-Benzyl[c]	II	160[e]	10	$C_{18}H_{23}NO\cdot HCl$					4.58	4.68
2	7300	.06[b]	6-Benzyl[c]	II	149[e]	48	$C_{18}H_{23}NO\cdot HCl$					4.58	4.58
3	14309	.06	4,6-Dibenzyl[c]	II	152[f]	..	$C_{25}H_{29}NO\cdot HCl$					3.54	3.54
4	7742	.21	4-Benzyl-6-methyl[d]	I	109[f]	50	$C_{19}H_{25}NO\cdot HCl$	71.34	71.12	8.19	8.18		
5	7295	.12t	4-Phenylhydroxymethyl	I	106[g]	59	$C_{18}H_{23}NO_2$					4.90	4.84
6	8049	.05i	4-(1-Methyl-1-phenylethyl)	I	150[h]	42	$C_{20}H_{27}NO\cdot HCl$					4.20	4.24
7	8996	.1t	4-(1-Methyl-1-phenylethyl)-6-hydroxy[c]	II	97[i]	35	$C_{20}H_{27}NO_2$	76.63	76.67	8.68	8.73		

[a] Q0.06 by D1 test. [b] Q0.09 by D1 test. [c] Intermediate phenol from Dow Chemical Company. [d] Analyses by Arlington Laboratories. [e] From isopropanol. [f] From ethyl acetate. [g] From ethanol. [h] From ethanol–ethyl acetate. [i] From ligroin.

TABLE V

MISCELLANEOUS 4-SUBSTITUTED α-DIETHYLAMINO-*o*-CRESOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7363	0.08i	0.4t	Methoxy[a]	IV		52	$C_{19}H_{19}NO_2$					6.69	6.77
2	7364	.06i	0.4	Ethoxy[b,c]	IV		66	$C_{19}H_{21}NO_2$					6.27	6.13
3	8371	.08		Benzyloxy	I	133[f]	37	$C_{18}H_{23}NO_2\cdot HCl$	67.17	67.13	7.51	7.51		
4	8048	.04	1.0i	Phenoxy[c]	III	130[g]	39	$C_{17}H_{21}NO_2\cdot HCl$					4.55	4.54
5		.05i		2,5-Dimethyl-1-pyrryl[d]	III	164[h]	25	$C_{17}H_{24}N_2O$	74.96	75.14	8.88	8.83		
6	8309	0.15		4'-Morpholinyl[c]	II	176[h]	..	$C_{18}H_{28}N_2O_2\cdot HCl$					9.31	9.31
7	7738	0.05		Cyano	II	208[h,i]	37	$C_{12}H_{16}N_2O\cdot HCl$					11.66	11.61
8	7637	.05i		Guanyl[e]		215[h]	68	$C_{12}H_{19}N_3O\cdot 2HCl$	48.98	49.30	7.20	7.10		

[a] Colorless liquid; b. p. 133–135° (3 mm.). [b] Slightly greenish colored liquid; b. p. 144–147° (3 mm.). [c] Intermediate phenol from Dow Chemical Company. [d] See Experimental Part for preparation of the intermediate phenol. [e] For preparation see experimental part. [f] From methyl ethyl ketone. [g] From isopropanol–ether. [h] From ethanol. [i] Light yellow-colored crystals.

cedures. Finally, after all the halide had been added, the mixture was heated at refluxing temperature and stirred for a total of twenty hours, at the end of which time nearly all the magnesium had dissolved.

To the Grignard reagent was added drop by drop with stirring 34 g. (0.26 mole) of diethylaminomethyl ethyl ether[6d] in 75 cc. of dry ether. Gentle refluxing was induced by the reaction. After all the ether solution had been added, the mixture was heated for an hour at refluxing temperature and then hydrolyzed with 250 cc. of 15% sulfuric acid. The acid layer was separated and rendered alkaline with excess concentrated sodium hydroxide solution. The product was extracted with ether and the ether extracts washed well with water and dried over anhydrous potassium carbonate. The filtered ether solution was treated with excess alcoholic hydrogen chloride. After the solvent was removed under reduced pressure, the residual mass crystallized. It was triturated with ether and the crystals collected.

4-Guanyl-α-diethylamino-*o*-cresol (V 8).—A rapid stream of dry hydrogen chloride gas was passed for an hour through an ice-cooled suspension of 10 g. (0.04 mole) of 4-cyano-α-diethylamino-*o*-cresol hydrochloride (V 7) in 100 cc. of absolute alcohol. After standing for twenty-four hours, the solution was evaporated to dryness at room temperature under reduced pressure. Twelve grams of a red crystalline powder, considered to be the corresponding crude imino ether dihydrochloride, was obtained; m. p. 158–168° with vigorous decomposition. [A small sample was recrystallized as nearly white crystals; m. p. 167–169° (dec.)].

Half (6 g.) of the crude imino ether salt was placed in a pressure bottle with a ten-fold excess of alcoholic ammonia and the mixture shaken for fourteen hours, after which time the ammonia was neutralized with alcoholic hydrogen chloride. Precipitated ammonium chloride was separated several different times during the evaporation of the solvent. It was removed by filtration. When the volume was reduced to about 15 cc., the desired product crystallized. After two recrystallizations from alcohol, with charcoal treatments, 4.0 g. of crystalline hydrochloride was obtained.

Pharmacological Results[20]

Among the many α-aminocresols from this Laboratory which have been screened in avian malarial infections, 128 of them are grouped in the ten tables of this paper in order to simplify a study of the relationships of structure to antimalarial activity. An indication of the therapeutic effect of each chemical is expressed numerically along with its survey number.[21]

In Table I, none of the compounds, all of which contain the tetramethylbutyl group, were found to be more active than the first. Of those in Table II, number 31 proved to be the most effective, possibly because of its chemical relationship to the active *o*-phenylphenol types (*e. g.*, III 20). While the O-acetyl derivative of (III 21) was nearly as

(20) The facilities for testing the compounds described in this paper were provided by the Office of Scientific Research and Development through the Committee on Medical Research and by Dr. A. L. Tatum of the Department of Pharmacology in the University of Wisconsin.

(21) The SN numbers are part of the system set up by the Survey Office of the National Research Council as a means of systematizing the various data reported from cooperating laboratories. B4 (*P. gallinaceum* in chicks), D1 (*P. lophurae* in ducks), D2 (*P. cathemerium* in ducks), and J1 (*P. cathemerium* in canaries) designate the avian test procedures of, respectively, Drs. R. J. Porter and L. T. Coggeshall; Dr. E. K. Marshall, Jr.; and Dr. A. L. Tatum. All infections are trophozoite induced. An indication of the therapeutic effect of each compound tested is expressed numerically as a quinine equivalent (q. equiv.). For example, 0.2 represents the activity of a drug that is one-fifth as a effective as quinine; 0.2i shows that a drug is inactive at five times the effective dose of quinine; and 0.2t designates a drug that is both toxic to the bird and inactive at five times the effective dose of quinine. Dr. Tatum usually reported activities without reference to quinine. In such cases, conversions were made by the authors for purposes of this report.

TABLE VI

FUSED RING α-AMINO-*o*-CRESOLS

No.	SN	Q. equiv B4		Name	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	7299	0.1	2.0	2-Diethylaminomethyl-1-naphthol	II	150[d]	57	$C_{15}H_{19}NO\cdot HCl$	67.78	67.72	7.53	7.14
2	6896		0.1t	1-Diethylaminomethyl-2-naphthol	I	164[e]	78	$C_{15}H_{19}NO\cdot HCl$	67.76	67.76	7.53	7.33
3		.05i	.33t	7-Dimethylaminomethyl-8-quinolinol	V	186[d]	74	$C_{13}H_{14}N_2O\cdot HCl$	60.37	60.16	6.33	6.43
4		.11		7-1′-Piperidylmethyl-8-quinolinol[a]	II	194[d]	52	$C_{15}H_{18}N_2O\cdot HCl$[c]	58.91	59.08	7.25	7.29
5			.33t	8-Diethylaminomethyl-7-quinolinol[b]	I	220[d]	37	$C_{14}H_{18}N_2O\cdot 2HCl$	55.45	55.19	6.65	6.33

[a] Free base (m. p. 117) prepared: German Patent 92,309; *Frdl.*, 4, 103 (1899). [b] Intermediate 7-quinolinol prepared by the directions of Skraup, *Monatsh.*, 5, 533 ("Beilstein," 10, 167). [c] Contains in addition 1.5 moles of water; *anal.* for N: calcd. 8.84. Found 8.79. [d] From ethanol. [e] From ethanol–acetone.

TABLE VII

α,α′-*bis*-(AMINO)-4,4′-BI-*o*-CRESOLS (DIHYDROCHLORIDES)[c]

No.	SN	Q. equiv. B4	J1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	6894	0.17t	0.5i	*bis*-(Diethylamino)	I	225[e]	55	$C_{23}H_{32}N_2O_2$	61.53	61.60	7.98	7.99
2	10271	4.0		α,α-*bis*-(Diethylamino)5,5′-bi-*o*-cresol[b]	II	106[e]	92	$C_{23}H_{32}N_2O_2$[d]	74.12	74.38	9.05	9.06
3	7824	0.75		6,6′-Dimethyl-*bis*-(diethylamino)[b]	I	215[f]	64	$C_{26}H_{36}N_2O_2$	63.00	62.63	8.37	8.18
4	7827	1.0		6,6′-Di-*n*-propyl-*bis*-(diethylamino)[b]	I	221[f]	70	$C_{28}H_{44}N_2O_2$	65.47	65.60	9.02	8.89
5		2.5		6,6′-Di-(2-chloroallyl)-*bis*-(diethylamino)[b]	I	208[g]	34	$C_{28}H_{38}Cl_2N_2O_2$	58.13	58.24	6.97	7.00
6	8379	0.11t		6,6′-Di-(2-methallyl)-*bis*-(diethylamino)[b]	I	263[f]	17	$C_{30}H_{44}N_2O_2$	67.02	66.70	8.62	8.76
7	8316	4.0	.5	6,6′-Diallyl-*bis*-(dimethylamino)[b]	I	241[g]	47	$C_{24}H_{32}N_2O_2$	63.56	63.26	7.56	7.53
8	6771	2.0	.5[a]	6,6′-Diallyl-*bis*-(diethylamino)	I	209[e]	67	$C_{28}H_{40}N_2O_2$	65.97	65.78	8.31	8.47
9	8315	1.0	.5	6,6′-Diallyl-*bis*-(di-*n*-propylamino)	I	187[g]	38	$C_{32}H_{48}N_2O_2$	67.94	67.99	8.91	8.92
10	8380	0.25		6,6′-Diallyl-*bis*-(di-*n*-butylamino)	I	178[g]	57	$C_{36}H_{56}N_2O_2$	69.54	69.60	9.40	9.46
11	9558	.5		6,6′-Diallyl-*bis*-(1-piperidyl)	I	250[f]	78	$C_{30}H_{40}N_2O_2$	67.52	67.20	7.93	7.99
12	10150	.05		6,6′-Diallyl-*bis*-(4-morpholinyl)	I	251[h]	70	$C_{22}H_{32}N_2O_4$	62.56	62.17	7.11	7.47
13	9187	.6		6,6′-Diallyl-*bis*-(2-hydroxyethyl)	I	111[i]	24	$C_{24}H_{32}N_2O_4$[d]	69.87	69.73	7.82	7.81
14	9188	.06		6,6′-Diallyl-*bis*-(di-2-hydroxyethyl)	I	130[j]	20	$C_{28}H_{40}N_2O_6$[d]	67.17	67.33	8.05	7.98
15	9635	1.3		0,0′-Diacetyl-6,6′-diallyl-*bis*-(diethylamino)	VI	224[k]	90	$C_{32}H_{44}N_2O_4$	64.74	64.81	7.81	7.75
16	11000	0.8		0,0′-Dipropionyl-6,6′-diallyl-*bis*-(diethylamino)	VI	185[l]	30	$C_{34}H_{48}N_2O_4$	65.68	65.42	8.10	8.37

[a] Q 0.5 by D1 and Q1–2 by D2. [b] Intermediate biphenol from Dow Chemical Company. [c] All compounds, except 2, 13 and 14, contain 2HCl. [d] Obtained as the free base. [e] From ethanol. [f] From methanol–acetone. [g] From ethanol–ether. [h] Ethanol–acetone. [i] From benzene. [j] From benzene–ethyl acetate. [k] From ether–ethyl acetate. [l] From ether–acetone.

TABLE VIII

bis-(α-DIETHYLAMINO-*o*-CRESOLS)

No.	SN	Q. Equiv B4	Name	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	5918	1.0[a]	4,4′-Oxy-*bis*-(α-diethylamino-*o*-cresol)[b,c]	99	66[g]	$C_{22}H_{32}N_2O_3$					7.52	7.51
2	8450	0.21	4,4′-Oxy-*bis*-(6-allyl-α-diethylamino-*o*-cresol)[b,d]	240	47[h]	$C_{28}H_{36}N_2O_3$[f]					5.97	5.99
3	7737	.09	4,4′-Isopropylidene-*bis*-(6-methyl-α-diethylamino-*o*-cresol)[d]	210	48[i]	$C_{27}H_{42}N_2O_2$[f]					5.61	5.56
4	9186	.5	4,4′-Isopropylidene-*bis*-(6-phenyl-α-diethylamino-*o*-cresol)[d,e]	75	77[j]	$C_{37}H_{46}N_2O_2$	80.68	80.01	8.42	8.67		
5	7828	.2	4,4′-[(α,β-Diethyl-α,β-dihydroxy)-ethylene]-*bis*-(α-diethylamino-*o*-cresol)[d]	153	23[h]	$C_{28}H_{44}N_2O_4$	71.14	70.87	9.38	9.51		
6	7826	.4	4,4′-[(α,β-Diethyl)-vinylene]-*bis*-(α-diethylamino-*o*-cresol)[d]	110	50[k]	$C_{28}H_{42}N_2O_2$	76.65	76.89	9.65	9.68		
7	8583	1.4	4,4′,4″,4‴-[Ethylenediethylidyne]-*tetrakis*-(α-diethylamino-*o*-cresol)[d,e]	150	6[l]	$C_{50}H_{74}N_4O_4$	75.52	75.25	9.38	9.36		

[a] Other activity figures: 1.0(J1), 0.09(D1) and 0.5(D2). [b] See Experimental part for the preparation of intermediate oxybiphenol. [c] Prepared by Procedure III. [d] Prepared by Procedure I. [e] Phenolic intermediate from Dow Chemical Company. [f] Contains also 2HCl. [g] From dilute ethanol. [h] From isopropanol. [i] From ethanol–ethyl acetate. [j] A suitable crystallizing solvent was not found; compound purified by neutralization of an acid solution. [k] From methanol. [l] From methanol–ethyl acetate.

active as the parent compound, the corresponding O-methyl compound (III 22) was both inactive and toxic at greater than the effective dosage of quinine. The benzyl-α-diethylamino-*o*-cresols (Table IV) appear to offer little promise. Despite their relationships to active types,[16,18] V 5 and 8

TABLE IX

α-DIETHYLAMINO-*p*-CRESOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Q. equiv. D1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	8999	0.04i			3,6-Dimethyl	II	104[a]	20	$C_{12}H_{19}NO$	75.31	75.10	10.21	10.08
2	9001	.05			3-Methyl-6-isopropyl[a]	II	93[f]	..	$C_{14}H_{23}NO$	76.54	76.69	10.71	10.61
3	6772	1.2	2.0	0.13	2-Phenyl[b]								
4	8050	0.4	2.0	.5i	2-Chloro-6-phenyl[c]	II	162[g]	80	$C_{17}H_{20}ClNO\cdot HCl$	62.58	62.61	6.49	6.70
5	8388	.4		.25t	2-Allyl-6-phenyl[d]	II	128[g]	66	$C_{20}H_{25}NO\cdot HCl$	72.38	72.33	7.90	8.10
6	10210	.12	1.0i		2,6-Diphenyl[c]	I	189[h]	57	$C_{23}H_{25}NO\cdot HCl$	75.08	75.14	7.12	7.14

[a] Microanalyses by Arlington Laboratories. [b] Preparation and proof of structure will appear in a later publication. [c] Intermediate phenol from Dow Chemical Company. [d] Intermediate 2-allyl-6-phenylphenol described by Auwers and Wittig, *J. prakt. Chem.*, [2] 108, 99 (1924). [e] From ligroin–acetone. [f] From ligroin. [g] From isopropanol. [h] From methanol–acetone.

TABLE X

POLY-(AMINOMETHYL)-PHENOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Name	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7357	0.05	0.17i	2,6-*bis*-(Dimethylaminomethyl)-phenol[a]									
2	7638	.06	.17i	2,4-*bis*-(Dimethylaminomethyl)-6-methylphenol[a]									
3	7736	.25		2,4-*bis*-(Diethylaminomethyl)-6-cyclohexylphenol[b,c]	199[e]	..	$C_{23}H_{38}N_2O\cdot 2HCl$	62.99	62.74	9.61	10.03	6.68	6.70
4	7358	1.8	.5	2,4-*bis*-(Diethylaminomethyl)-6-phenylphenol[b,c]	207[f]	95	$C_{23}H_{34}N_2O\cdot 2HCl$	63.91	63.58	8.29	8.35		
5	7356	0.23		2,5-*bis*-(Diethylaminomethyl)-hydroquinone[d]	107[f]	62	$C_{18}H_{34}N_2O_2$	68.53	68.46	10.07	9.81	9.99	9.83
6	6793	.03	.17i	2,4,6-*tris*-Dimethylaminomethyl)-phenol[a]									
7	6795	.02i		2,4,6-*tris*-(4-morpholinylmethyl)-phenol[a]									

[a] Sample from Rohm and Haas Company. [b] Intermediate phenol from Dow Chemical Company. [c] Prepared by Procedure I. [d] Prepared by Procedure II. [e] From ethyl acetate. [f] From alcohol.

were ineffective. VI 1 was twice as active as quinine in the canary; this effectiveness demonstrates how the α-aminocresol grouping may confer antimalarial activity upon compounds containing various nuclei. The bis-(dialkylamino)-bi-*o*-cresols of Table VII offer evidence of nuclear variations that increase activity. Although the efficacy of VIII 1 in avian malaria has been of considerable interest, the nuclear introduction of allyl groups patterned after the VII 7 series resulted in the inactive compound VIII 2. The only compounds of note in Tables IX and X were derived from *o*-phenylphenol.

Detailed pharmacological data on all the compounds included in this paper will appear elsewhere, along with descriptions of the testing methods used. Also, clinical reports on several of the compounds will be published elsewhere.

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Summary

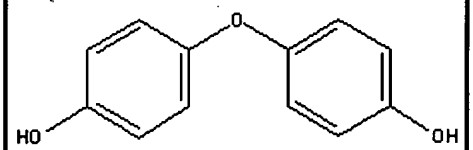
Establishment of the effectiveness of α-dimethylamino-4-(1,1,3,3-tetramethylbutyl)-*o*-cresol in avian malaria has resulted in the synthesis and study of hundreds of compounds. This first report includes 128 compounds, most of which were prepared by the Mannich reaction; 109 are new. For the purpose of studying the relationships of chemical structure to activity, the compounds have been classified in ten tables.

Several of these agents range in effectiveness from one to four times that of quinine. The following are representative of some of the most interesting types thus far prepared in this particular group: 4-*t*-butyl-α-diethylamino-6-phenyl-*o*-cresol, 2-diethylaminomethyl-1-naphthol, 6,6′-diallyl-α,α′-*bis*-(dimethylamino)-4,4′-bi-*o*-cresol, and 4,-4′-oxy-*bis*-(α-diethylamino-*o*-cresol).

DETROIT, MICHIGAN RECEIVED APRIL 22, 1946

4,4'-Oxydiphenol [1965-09-9]

Synonyms: 4,4'-Dihydroxydiphenyl ether; 4,4[-Oxydiphenol; 4,4'-Oxydiphenol;



Formula	$C_{12}H_{10}O_3$	Molecular Weight	202.2092
CAS RN	1965-09-9	Melting Point (°C)	167 - 169
ACX Number	X1034496-2	Boiling Point (°C)	
Density		Vapor Density	
Refractive Index		Vapor Pressure	
Evaporation Rate		Water Solubility	
Flash Point (°C)		EPA Code	
DOT Number		RTECS	SM6040000
Comments			

More information about the chemical is available in these categories:

Physical Properties (1)
NIST Chemistry WebBook
Information about this particular compound

Trading (1)
Available Chemicals Exchange
Information about this particular compound

09763499

TI Aminoalkylphenols as antimalarials. I. Simply substituted α-aminocresols

SO Journal of the American Chemical Society (1946), 68, 1894-1901
CODEN: JACSAT; ISSN: 0002-7863

IT Phenols
(aminoalkyl, as antimalarials)

IT Malaria
(antimalarial compds., (aminoalkyl) phenols as)

IT 93-92-5P, Acetic acid, α-methylbenzyl ester 120-65-0P, o-Cresol, α-dimethylamino- 493-75-4P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(diethylamino)- 515-59-3P, Sulfamethylthiazole 1138-39-2P, o-Cresol, 4-tert-butyl-α-dimethylamino-, hydrochloride 1965-09-9P, Phenol, 4,4'-oxydi- 3624-96-2P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(diethylamino)-, dihydrochloride 5392-14-3P, o-Cresol, α-dimethylamino-4-(1,1,3,3 tetramethylbutyl)- 5414-76-6P, Ethanol, 2-(3-phenylsalicylamino)- 5414-83-5P, o-Cresol, α-piperidino-4-(1,1,3,3-tetramethylbutyl)- 5424-68-0P, 2,5-Xylohydroquinone, α2,α5-bis(diethylamino)- 5425-76-3P, o-Cresol, 4-chloro-α-diethylamino-, hydrochloride 6452-87-5P, o-Cresol, α-morpholino-4-phenyl- 6639-10-7P, o-Cresol, 4-tert-butyl-α-dimethylamino-6-phenyl-, hydrochloride 7494-55-5P, o-Cresol, 4,4'-oxybis[α-diethylamino- 13704-50-2P, o-Cresol, 4-chloro-α-piperidino- 17915-35-4P, 2,6-Xylenol, α-diethylamino- 18942-90-0P, Acetic acid, α-methylnitrobenzyl ester 20484-31-5P, 2,4-Xylenol, α2-diethylamino- 20484-34-8P, o-Cresol, 4-tert-butyl-α-diethylamino- 21140-37-4P, o-Cresol, α-dimethylamino-4-phenyl- 23473-74-7P, Phenol, 2-allyl-4-tert-butyl- 23562-78-9P, o-Cresol, α-diethylamino-4-methoxy- 23802-11-1P, 2,6-Xylenol, α-dimethylamino- 54609-09-5P, Phenol, p-(2,5-dimethyl-1-pyrrolyl)- 66839-99-4P, o-Cresol, 4-phenyl-α-piperidino- 69286-57-3P, Phenol, 4-(diethylaminomethyl)-2,5-dimethyl- 71119-13-6P, Acetanilide, 4'-[(4-methyl-2-thiazolyl)sulfamoyl]- 77895-37-5P, 8-Quinolinol, 7-(dimethylaminomethyl)-, hydrochloride 77895-39-7P, 8-Quinolinol, 7-piperidinomethyl-, hydrochloride 82364-54-3P, 2-Naphthol, 1-(diethylaminomethyl)-, hydrochloride 83953-63-3P, Ethanol, 2,2'-[5-(1,1,3,3-tetramethylbutyl)salicylimino]di- 86393-73-9P, 2,6-Xylenol, α-dimethylamino-4-(1,1,3,3-tetramethylbutyl)- 87059-85-6P, 2,5-Xylenol, 4-chloro-α2-piperidino- 93723-22-9P, o-Cresol, α-diethylamino-6-phenyl- 109247-39-4P, 2,6-Xylenol, α-diethylamino-α'-phenyl-, hydrochloride 110491-38-8P, 2,4-Xylenol, α2-diethylamino-α4-phenyl-, hydrochloride 123774-74-3P, o-Cresol, α-amino-4-phenyl- 128236-87-3P, o-Cresol, α-amino-4-phenyl-, hydrochloride 158550-19-7P, 6-m-Cymenol, 7-diethylamino-8-phenyl-, hydrochloride 178426-62-5P, 4,4'-Bi-o-cresol, 6,6'-bis(2-chloroallyl)-α,α'-bis(diethylamino)-, dihydrochloride 178426-64-7P, 4,4'-Bi-o-cresol, α,α'-bis(diethylamino)-6,6'-bis(2-methylallyl)-, dihydrochloride 725227-28-1P, Anisole, 2-bromo-4-tert-butyl-6-phenyl- 725232-42-8P, Anisole, 4-tert-butyl-2-phenyl- 790595-24-3P, p-Cresol, α-diethylamino-2-phenyl- 854181-04-7P, Benzylamine, 5-tert-butyl-N,N-diethyl-2-methoxy-3-phenyl-, hydrochloride 854211-58-8P, Ethanol, 2,2'-[(5,5'-diallyl-4,4'-dihydroxy-3,3'-biphenylene)bis(methyleneimino)]di- 854211-60-2P, Ethanol, 2,2',2'',2'''-[(5,5'-diallyl-4,4'-dihydroxy-3,3'-biphenylene)bis(methylenenitrilo)]tetra- 854824-59-2P, 5,6-m-Cymenediol, 7-diethylamino-8-phenyl- 855347-02-3P, o-Cresol, 6-allyl-α-diethylamino-4-(1,1-dimethylpropyl)-, hydrochloride 855347-04-5P, o-Cresol, 6-allyl-4-cyclohexyl-α-diethylamino-, hydrochloride

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855347-12-5P, o-Cresol, 6-allyl-4-tert-butyl-α-diethylamino-, hydrochloride 855347-40-9P, o-Cresol, 6-bromo-α-diethylamino-4-phenyl-, hydrochloride 855347-42-1P, o-Cresol, 4-bromo-α-diethylamino-6-phenyl-, hydrochloride 855347-46-5P, o-Cresol, 6-bromo-4-cyclohexyl-α-diethylamino- 855350-18-4P, o-Cresol, 4,4'-[1,4-bis(α-diethylamino-4-hydroxy-m-tolyl)-1,4-dimethyltetramethylene]bis[α-diethylamino- 855350-18-4P, Hexane, 2,2,5,5-tetrakis(α-diethylamino-4-hydroxy-m-tolyl)- 855350-20-8P, o-Cresol, 4-(benzyloxy)-α-diethylamino-, hydrochloride 855350-79-7P, o-Cresol, 4-tert-butyl-α-diethylamino-5-phenyl-, hydrochloride 855350-83-3P, o-Cresol, 4-tert-butyl-6-cyclohexyl-α-diethylamino-, hydrochloride 855351-03-0P, o-Cresol, 6-chloro-4-phenyl-α-piperidino- 855351-21-2P, o-Cresol, 6-chloro-α-diethylamino-4-(1,1,3,3-tetramethylbutyl)- 855351-23-4P, o-Cresol, 6-chloro-α-diethylamino-5-phenyl-, hydrochloride 855351-25-6P, o-Cresol, 6-chloro-α-diethylamino-4-phenyl-, hydrochloride 855351-53-0P, o-Cresol, α-decylamino-6-phenyl-, hydrochloride 855351-63-2P, o-Cresol, 4-tert-butyl-α-ethylamino-6-phenyl-, hydrochloride 855351-81-4P, o-Cresol, α-diethylamino-6-phenyl-4-(1,1,3,3-tetramethylbutyl)-, hydrochloride 855351-83-6P, o-Cresol, α-diethylamino-5-phenyl- 855351-85-8P, o-Cresol, α-diethylamino-4-phenyl-, hydrochloride 855351-89-2P, o-Cresol, α-diethylamino-4-octyl-, hydrochloride 855351-91-6P, o-Cresol, α-diethylamino-4-morpholino-, hydrochloride 855351-93-8P, o-Cresol, α-diethylamino-4-(2-methylcyclohexyl)-, hydrochloride 855351-95-0P, o-Cresol, α-diethylamino-6-(1-methylallyl)-4-phenyl-, hydrochloride 855354-16-4P, o-Cresol, α-dipentylamino-4-(1,1,3,3-tetramethylbutyl)-, hydrobromide 855354-17-5P, o-Cresol, α-dipentylamino-4-(1,1,3,3-tetramethylbutyl)- 855354-50-6P, o-Cresol, α-diethylamino-6-heptyl-, hydrochloride 855354-52-8P, o-Cresol, α-diethylamino-4-ethoxy- 855354-54-0P, o-Cresol, α-diethylamino-4-dodecyl- 855354-56-2P, o-Cresol, α-diethylamino-4-(2,5-dimethyl-1-pyrrolyl)- 855354-58-4P, o-Cresol, α-diethylamino-4-(1,1-dimethylpropyl)-6-phenyl-, hydrochloride 855354-61-9P, o-Cresol, α-diethylamino-, hydrochloride 855354-69-7P, o-Cresol, 4,4'-isopropylidenebis[α-diethylamino-6-phenyl- 855358-10-0P, o-Cresol, α-morpholino-4-(1,1,3,3-tetramethylbutyl)-, hydrochloride 855358-20-2P, p-Cresol, 2-allyl-α-diethylamino-6-phenyl-, hydrochloride 855358-50-8P, p-Cresol, 2-chloro-α-diethylamino-6-phenyl-, hydrochloride 855407-25-9P, Phenol, 2-(diethylaminomethyl)-3,5,6-trimethyl-, hydrochloride 855626-75-4P, Phenol, 4,4'-oxybis[3-allyl- 856081-13-5P, 1-Naphthol, 2-(diethylaminomethyl)-, hydrochloride 856181-28-7P, o-Cresol, 6-chloro-α-diethylamino-4-(1,1-dimethylpropyl)-, hydrochloride 856181-31-2P, o-Cresol, 4-chloro-α-diethylamino-6-(1-methylallyl)-, hydrochloride 856181-54-9P, o-Cresol, α-dibenzylamino-4-(1,1,3,3-tetramethylbutyl)- 856182-03-1P, o-Cresol, α-ethylamino-6-phenyl-, hydrochloride 856188-82-4P, Mesitol, α2-diethylamino-α4,α6-diphenyl-, hydrochloride 856372-15-1P, Ethanol, 2-(5-tert-butyl-3-phenylsalicylamino)-, hydrochloride 856375-37-6P, Ethanol, 2-[ethyl[5-(1,1,3,3-tetramethylbutyl)salicyl]amino]-, hydrochloride 856375-48-9P, Ethanol, 2-[ethyl(5-phenylsalicyl)amino]-, hydrochloride 856999-83-2P, Thymol, 6-(diethylaminomethyl)- 856999-83-2P, 3,4-Xylenol, α4-diethylamino-6-isopropyl- 857008-67-4P, m-Tolunitrile, α-diethylamino-4-hydroxy-, hydrochloride 857417-23-3P, Pyrocatechol, 3-(diethylaminomethyl)-5-phenyl- 857425-93-5P, Pyrocatechol, 5-tert-butyl-3-(diethylaminomethyl)- 857755-79-4P, 4,4'-Stilbenediol, 3,3'-bis(diethylaminomethyl)-α,α'-diethyl- 858197-63-4P, Mesitol, α2-diethylamino-

α4-phenyl- 858811-58-2P, 5,5'-Bi-o-cresol, α,α'-bis(diethylamino)- 859329-21-8P, Ammonium, trimethyl[5-(1,1,3,3-tetramethylbutyl)salicyl]-, chloride 859781-72-9P, 2,3-Xylenol, 4-chloro-α2-diethylamino-6-hexyl-, hydrochloride 859782-62-0P, 2,5-Xylenol, 4-chloro-α2-morpholino-, hydrochloride 859782-65-3P, 2,5-Xylenol, 4-chloro-α2-diethylamino-, hydrochloride 859782-71-1P, 2,5-Xylenol, 4-tert-butyl-α2-diethylamino-, hydrochloride 859782-96-0P, 2,4-Xylenol, 6-bromo-α2-diethylamino-, hydrochloride 859783-20-3P, 2,6-Xylenol, 4-tert-butyl-α-diethylamino-, hydrochloride 859783-41-8P, 2,6-Xylenol, 4-bromo-α-diethylamino-, hydrochloride 859783-48-5P, 2,4-Xylenol, α2-diethylamino-, hydrochloride 859783-53-2P, 2,4-Xylenol, 6-cyclohexyl-α2,α4-bis(diethylamino)-, dihydrochloride 859783-96-3P, 2,6-Xylenol, 4,4'-isopropylidenebis[α-diethylamino-, dihydrochloride 859791-02-9P, m-Toluimidic acid, α-diethylamino-4-hydroxy-, Et ester, dihydrochloride 860233-56-3P, 7-Quinolinol, 8-(diethylaminomethyl)-, dihydrochloride 860254-88-2P, Hydrobenzoin, 3,3'-bis(diethylaminomethyl)-α,α'-diethyl-4,4'-dihydroxy- 875853-64-8P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(diethylamino)-, dipropionate 875853-64-8P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(diethylamino)-, dipropionate 875853-71-7P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(diethylamino)-, diacetate 875853-71-7P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(diethylamino)-, diacetate 878754-86-0P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(dipropylamino)-, dihydrochloride 878754-87-1P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(dimethylamino)-, dihydrochloride 878754-88-2P, 4,4'-Bi-o-cresol, 6,6'-diallyl-α,α'-bis(dibutylamino)-, dihydrochloride 878756-21-9P, 4,4'-Bi-2,6-xylenol, α,α''-bis(diethylamino)-, dihydrochloride 878760-11-3P, o-Cresol, 4-chloro-α-diethylamino-6-phenyl-, hydrochloride 878760-61-3P, o-Cresol, α-diethylamino-4-phenoxy-, hydrochloride 878785-12-7P, 2,4-Xylenol, α2,α4-bis(diethylamino)-6-phenyl-, dihydrochloride 878785-13-8P, 2,6-Xylenol, α-diethylamino-, hydrochloride
RL: PREP (Preparation)
(preparation of)

L8 ANSWER 4 OF 15 USPATFULL on STN

ACCESSION NUMBER:	1999:137252 USPATFULL			
TITLE:	Substituted imidazole compounds			
INVENTOR(S):	Adams, Jerry L., Wayne, PA, United States Boehm, Jeffrey C., King of Prussia, PA, United States Lee, Dennis, Swarthmore, PA, United States			
PATENT ASSIGNEE(S):	SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5977103		19991102	
	WO 9725045		19970717	<--
APPLICATION INFO.:	US 1998-101531		19981113	(9)
	WO 1997-US500		19970110	
			19981113	PCT 371 date
			19981113	PCT 102(e) date
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Ramsuer, Robert W.			
LEGAL REPRESENTATIVE:	Dinner, Dara L., Venetianer, Stephen, Kinzig, Charles			

M.
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 2761
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5977103 19991102
WO 9725045 19970717 <--
SUMM . . . and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and. . .
DETD . . . other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft. . .
CLM What is claimed is:
. . . condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerularnephritis, diabetes,. . .
IT 90-05-1, 2-Methoxyphenol 92-69-3, [1,1'-Biphenyl]-4-ol 98-17-9, 3-Trifluoromethylphenol 103-16-2, 4-Benzyloxyphenol 106-44-5, 4-Methylphenol, reactions 106-48-9, 4-Chlorophenol 108-46-3, Resorcinol, reactions 108-95-2, Phenol, reactions 120-80-9, Catechol, reactions 123-00-2, 4-(3-Aminopropyl)morpholine 123-07-9, 4-Ethylphenol 123-31-9, 1,4-Benzenediol, reactions 150-19-6, 3-Methoxyphenol 150-76-5, 4-MethoxyPhenol 367-12-4, 2-Fluorophenol 371-41-5, 4-FluoroPhenol 372-20-3, 3-Fluorophenol 459-57-4, 4-Fluorobenzaldehyde 533-31-3, Sesamol 576-26-1, 2,6-Dimethylphenol 619-57-8, 4-Hydroxybenzamide 767-00-0, 4-Cyanophenol 824-79-3, Sodium p-toluenesulfinate 831-82-3, 4-Phenoxyphenol 2713-33-9, 3,4-Difluorophenol 4746-97-8, 1,4-Cyclohexanedione monoethylene ketal 6313-54-8, 2-Chloro-4-pyridinecarboxylic acid 6342-56-9, Pyruvic aldehyde dimethyl acetal 13183-79-4, 5-Mercapto-1-methyltetrazole 14763-60-1, 4-Methylsulfonylphenol 79099-07-3, 1-tert-Butoxycarbonyl-4-piperidinone
(preparation of pyrimidinylimidazoles and analogs as drugs)

L8 ANSWER 5 OF 15 USPATFULL on STN
ACCESSION NUMBER: 1998:82359 USPATFULL
TITLE: Enhanced skin penetration system for improved topical delivery of drugs
INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States
PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5780049		19980714	<--
APPLICATION INFO.:	US 1995-464991		19950605 (8)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No.			

US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rose, Shep K.
LEGAL REPRESENTATIVE: Henderson, Loretta J., Dabbiere, David K.
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 698
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5780049 19980714 <--
SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.
IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.13,7]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
(antimicrobial topical compns. containing polyacrylamide and)

L8 ANSWER 6 OF 15 USPATFULL on STN
ACCESSION NUMBER: 1998:78738 USPATFULL
TITLE: Enhanced skin penetration system for improved topical delivery of drugs
INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States
PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5776485		19980707	<--
APPLICATION INFO.:	US 1995-469701		19950606	(8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rose, Shep K.
LEGAL REPRESENTATIVE: Henderson, Loretta J., Dabbiere, David K.
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1

LINE COUNT: 700
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5776485 19980707 <--
SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.
IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.13,7]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
(antimicrobial topical compns. containing polyacrylamide and)

L8 ANSWER 7 OF 15 USPATFULL on STN
ACCESSION NUMBER: 1998:75609 USPATFULL
TITLE: Indane and tetrahydronaphthalene derivatives as calcium channel antagonists
INVENTOR(S): Harling, John David, Essex, England
Orlek, Barry Sidney, Essex, England
PATENT ASSIGNEE(S): SmithKline Beecham p.l.c., Brentford, England (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5773463		19980630	<--
	WO 9504028		19950209	<--
APPLICATION INFO.:	US 1996-583026		19960122	(8)
	WO 1994-EP2409		19940721	
			19960122	PCT 371 date
			19960122	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1993-15566	19930728

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Hall, Linda E., Venetianer, Stephen A., Lentz, Edward T.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 1913
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5773463 19980630 <--
WO 9504028 19950209 <--
SUMM . . . recited hereinabove and R.sub.4 is oxy or thio, which compounds are said to be useful for the treatment of drug-resistant malaria and other drug-resistant protozoal infections.
IT 62-53-3, Aniline, reactions 67-64-1, Acetone, reactions 91-60-1, 2-Naphthalenethiol 92-69-3, 4-Phenylphenol 95-13-6, Indene 95-76-1, 3,4-Dichloroaniline 98-54-4, 4-tert-Butylphenol 103-16-2, 4-Benzyloxyphenol 108-95-2, Phenol, reactions 108-98-5, Thiophenol,

reactions 110-53-2, 1-Bromopentane 330-93-8, Bis(4-fluorophenyl) ether 345-83-5, 4-Fluorobenzophenone 345-92-6, 4,4'-Difluorobenzophenone 402-44-8, 4-Fluorobenzotrifluoride 541-41-3, Ethyl chloroformate 580-51-8, 3-Phenylphenol 831-82-3, 4-Phenoxyphenol 1137-41-3, 4-Aminobenzophenone 1194-02-1, 4-Fluorobenzonitrile 1435-49-0, 1,2-Dichloro-4-fluorobenzene 5858-17-3, 3,4-Dichlorothiophenol 7182-29-8 7182-32-3, 2-Phenyl-5-methoxybenzo[b]furan 28059-64-5, 2-Benzylaniline 28994-41-4, 2-Hydroxydiphenylmethane 54957-94-7, tert-Butyl N,N-dichlorocarbamate 75287-72-8 88400-85-5
(preparation of aminoindanes and -tetrahydronaphthalenes as calcium channel antagonists)

L8 ANSWER 8 OF 15 USPATFULL on STN
ACCESSION NUMBER: 1998:75176 USPATFULL
TITLE: Enhanced skin penetration system for improving topical delivery of drugs
INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States
PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5773023		19980630	<--
APPLICATION INFO.:	US 1995-462710		19950605	(8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rose, Shep K.
LEGAL REPRESENTATIVE: Henderson, Loretta J., Dabbiere, David K.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
LINE COUNT: 745
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5773023 19980630 <--
SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.
CLM What is claimed is:
. . . diuretic drugs, vasodilator drugs, vasoconstrictor drugs, anti-ulcer drugs, anesthetic drugs, antidepressant drugs, tranquilizer and sedative drugs, antipsychotic drugs, antineoplastic drugs, antimalarial drugs, muscle relaxant drugs, antispasmodic drugs, antidiarrheal drugs, bone-active drugs and mixtures thereof; and (c) from about 0.05% to about. . .
IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0

768-94-5, Tricyclo[3.3.1.13,7]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
(antimicrobial topical compns. containing polyacrylamide and)

L8 ANSWER 9 OF 15 USPATFULL on STN
ACCESSION NUMBER: 1998:57923 USPATFULL
TITLE: Substituted imidazole compounds
INVENTOR(S): Adams, Jerry L., Wayne, PA, United States
Boehm, Jeffrey C., King of Prussia, PA, United States
Lee, Dennis, Swarthmore, PA, United States
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5756499		19980526	<--
APPLICATION INFO.:	US 1997-780954		19970110	(8)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1996-609907P	19960111	(60)
	US 1996-814952P	19960405	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ramsuer, Robert W.
LEGAL REPRESENTATIVE: Dinner, Dara L., Venetianer, Stephen, Lentz, Edward T.
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
LINE COUNT: 2845
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5756499 19980526 <--
SUMM . . . and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and. . .
DETD . . . other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft. . .
CLM What is claimed is:
. . . septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerularonephritis, diabetes,. . .
. . . septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal

reperfusion injury, thrombosis, glomerularnephritis, diabetes,. . .
IT 62-56-6, Thiourea, reactions 90-05-1, 2-Methoxyphenol 92-69-3, 4-Phenylphenol 98-17-9, 3-Trifluoromethylphenol 103-16-2, 4-Benzyloxyphenol 106-44-5, 4-Methylphenol, reactions 106-48-9, 4-Chlorophenol 108-46-3, 1,3-Benzenediol, reactions 108-95-2, Phenol, reactions 108-98-5, Benzenethiol, reactions 120-80-9, Catechol, reactions 123-00-2, N-(3-Aminopropyl)morpholine 123-07-9, 4-Ethylphenol 123-31-9, 1,4-Benzenediol, reactions 150-19-6, 3-Methoxyphenol 150-76-5, 4-Methoxyphenol 367-12-4, 2-Fluorophenol 371-41-5, 4-Fluorophenol 372-20-3, 3-Fluorophenol 459-57-4, p-Fluorobenzaldehyde 533-31-3, Sesamol 576-26-1 619-57-8, 4-Hydroxybenzamide 767-00-0, 4-Cyanophenol 824-79-3, p-Toluenesulfinic acid sodium salt 831-82-3 2713-33-9, 3,4-Difluorophenol 4637-24-5 4746-97-8, 1,4-Cyclohexanedione monoethylene ketal 6313-54-8, 2-Chloro-4-pyridinecarboxylic acid 6342-56-9, Pyruvic aldehyde dimethyl acetal 13183-79-4, 5-Mercapto-1-methyltetrazole 14763-60-1, 4-Methylsulfonylphenol 79099-07-3, 1-tert-Butoxycarbonylpiperidin-4-one
(preparation of substituted imidazoles as cytokine inhibitors)

L8 ANSWER 10 OF 15 USPATFULL on STN
ACCESSION NUMBER: 1998:57546 USPATFULL
TITLE: Enhanced skin penetration system for improved topical delivery of drugs
INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States
PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5756119		19980526	<--
APPLICATION INFO.:	US 1995-462376		19950605 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rose, Shep K.
LEGAL REPRESENTATIVE: Henderson, Loretta J., Dabbiere, David K.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 697
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5756119 19980526 <--
SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.
IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0

768-94-5, Tricyclo[3.3.1.13,7]decan-1-amine 914-00-1, Methacycline
1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5,
Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline
11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin
37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin
85721-33-1, Ciprofloxacin
(antimicrobial topical compns. containing polyacrylamide and)

L8 ANSWER 11 OF 15 USPATFULL on STN
ACCESSION NUMBER: 1998:57545 USPATFULL
TITLE: Enhanced skin penetration system for improved topical delivery of drugs
INVENTOR(S): Deckner, George Endel, Trumbull, CT, United States
Lombardo, Brian Scott, Ansonia, CT, United States
PATENT ASSIGNEE(S): Richardson-Vicks Inc., Shelton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5756118		19980526	<--
APPLICATION INFO.:	US 1995-462258		19950605 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1995-390902, filed on 16 Feb 1995, now abandoned which is a continuation of Ser. No. US 1994-228167, filed on 15 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-111032, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1992-957752, filed on 2 Oct 1992, now abandoned which is a continuation of Ser. No. US 1991-778424, filed on 16 Oct 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rose, Shep K.
LEGAL REPRESENTATIVE: Henderson, Loretta J., Dabbiere, David K.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 682
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5756118 19980526 <--
SUMM Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.
IT 55-56-1, Chlorhexidine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 59-01-8, Kanamycin 74-55-5, Ethambutol 79-57-2, Oxytetracycline 100-33-4, Pentamidine 100-97-0, biological studies 154-21-2 443-48-1, Metronidazole 564-25-0 768-94-5, Tricyclo[3.3.1.13,7]decan-1-amine 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 3380-34-5, Triclosan 7542-37-2, Paromomycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 22916-47-8, Miconazole 32986-56-4, Tobramycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 70458-96-7, Norfloxacin 85721-33-1, Ciprofloxacin
(antimicrobial topical compns. containing polyacrylamide and)

L8 ANSWER 12 OF 15 USPATFULL on STN
ACCESSION NUMBER: 93:26884 USPATFULL
TITLE: Oral osmotic device
INVENTOR(S): Edgren, David E., El Granada, CA, United States

	Bhatti, Gurdish K., Fremont, CA, United States
PATENT ASSIGNEE(S):	ALZA Corporation, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5200194		19930406	<--
APPLICATION INFO.:	US 1991-809741		19911218	(7)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Page, Thurman K.
ASSISTANT EXAMINER:	Horne, Leon R.
LEGAL REPRESENTATIVE:	Duvall, Jean M., Miller, D. Byron, Stone, Steven F.
NUMBER OF CLAIMS:	19
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	880

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5200194 19930406 <--

DETD . . . sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatory drugs, local anesthetics, muscle contractants, anti-plaque agents, anti-microbials, anti-fungals, anti-malarials, hormonal agents, contraceptives, sympathomimetics, diuretics, anti-parasitics, neoplastics, hypoglycemics, ophthalmics, electrolytes, diagnostic agents, and cardiovascular drugs.

IT 54-21-7, Sodium salicylate 56-95-1, Chlorhexidine diacetate 64-17-5, Ethanol, biological studies 69-05-6, Mepacrine hydrochloride 69-65-8, Mannitol 87-99-0, Xylitol 89-83-8, Thymol 122-18-9, Cetyldimethylbenzylammonium chloride 123-03-5, Cetylpyridinium chloride 134-50-9 522-51-0, Dequalinium chloride 532-32-1, Sodium benzoate 546-46-3, Zinc citrate 614-87-9 637-32-1, Proguanil hydrochloride 1330-43-4, Boron sodium oxide (B4Na2O7) 2447-54-3, Sanguinarine 3380-34-5, Triclosan 3697-42-5 5578-73-4, Sanguinarine chloride 7681-49-4, Sodium fluoride, biological studies 7722-84-1, Hydrogen peroxide, biological studies 7783-47-3, Stannous fluoride 9001-37-0, Glucose oxidase 9032-08-0 9075-84-7, Mutanase 15593-49-4 18472-51-0, Hexidine 22573-93-9, Alexidine 60406-21-5 62571-86-2 71251-02-0, Octenidine 79874-76-3, Decapinol
(therapeutic oral osmotic device containing)

L8 ANSWER 13 OF 15 USPATFULL on STN

ACCESSION NUMBER:	93:18693 USPATFULL
TITLE:	Pyrazole-containing juvenile hormone mimics for pest control
INVENTOR(S):	Bowers, William S., Tucson, AZ, United States Sugiyama, Takeyoshi, Sendai, Japan
PATENT ASSIGNEE(S):	Arizona Board of Regents Acting for the University of Arizona, Tucson, AZ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5192787		19930309	<--
APPLICATION INFO.:	US 1990-538422		19900615	(7)

RELATED APPLN. INFO.:	Division of Ser. No. US 1988-284394, filed on 14 Dec 1988, now patented, Pat. No. US 4943586
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Brust, Joseph Paul

ASSISTANT EXAMINER: Gabilan, Mary Susan H.
LEGAL REPRESENTATIVE: Oblon, Spivak, McClelland, Maier & Neustadt
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 442
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5192787 19930309 <--
DETD Malaria mosquito, Anopheles quadrimaculatus
CLM What is claimed is:
. . . insect is selected from the group consisting of American cockroach, Periplaneta americana German cockroach, Blattella germanica Yellowfever mosquito, Aedes aegypti Malaria mosquito, Anopheles quadrimaculatus Northern house mosquito, Culex pipens House fly, Musca domestica House cricket, Acheta domesticus Corn earworm, Heliothis zea.
. . .
IT 831-82-3, 4-Phenoxyphenol
(condensation of, with active bromoacetate)

L8 ANSWER 14 OF 15 USPATFULL on STN
ACCESSION NUMBER: 90:57814 USPATFULL
TITLE: Pyrazole-containing juvenile hormone mimics for pest control, compositions and use
INVENTOR(S): Bowers, William S., Tucson, AZ, United States
Sugiyama, Takeyoshi, Sendai, Japan
PATENT ASSIGNEE(S): Arizona Board of Regents for the University of Arizona, Tucson, AZ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4943586		19900724	<--
APPLICATION INFO.:	US 1988-284394		19881214	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ramsuer, Robert W.
LEGAL REPRESENTATIVE: Oblon, Spivak, McClelland, Maier & Neustadt
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1,10
LINE COUNT: 410
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4943586 19900724 <--
DETD Malaria mosquito, Anopheles quadrimaculatus
CLM What is claimed is:
. . . insect is selected from the group consisting of American cockroach, Periplaneta americana German cockroach, Blattella germanica Yellowfever mosquito, Aedes aegypti Malaria mosquito, Anopheles quadrimaculatus Northern house mosquito, Culex pipens House fly, Musca domestica House cricket, Acheta domesticus Corn earworm, Heliothis zea.
IT 831-82-3, 4-Phenoxyphenol
(condensation of, with active bromoacetate)

L8 ANSWER 15 OF 15 USPATFULL on STN
ACCESSION NUMBER: 85:25417 USPATFULL
TITLE: Oxime ethers and their use
INVENTOR(S): Ohsumi, Tadashi, Funabashi, Japan
Hatakoshi, Makoto, Minoo, Japan
Kisida, Hirosi, Takarazuka, Japan
PATENT ASSIGNEE(S): Sumitomo Chemical Company, Limited, Osaka, Japan (non-U.S. corporation)

09763499

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4514406		19850430	<--
APPLICATION INFO.:	US 1983-466905		19830216	(6)

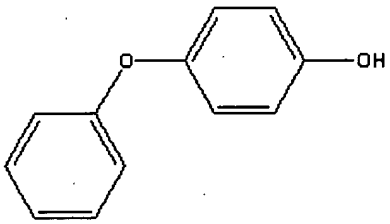
	NUMBER	DATE
PRIORITY INFORMATION:	JP 1982-34553	19820304

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Trousof, Natalie
ASSISTANT EXAMINER: Hendriksen, Leah
LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1,12
LINE COUNT: 924
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4514406 19850430 <--
DETD housefly (Musca domestica), melon fly (Dacus cucurbitae), common mosquito (Culex pipiens pallens), yellow fever mosquito (Aedes aegypti), malaria mosquito (Anopheles sp.), etc.
IT [redacted]831-82-3
(alkylation of, by propionaldoxime derivative)

Jagoe

4-Phenoxyphenol [831-82-3]

Synonyms: 4-Phenoxyphenol;



Formula	$C_{12}H_{10}O_2$	Molecular Weight	186.2098
CAS RN	831-82-3	Melting Point (°C)	83 - 85
ACX Number	X1006175-7	Boiling Point (°C)	177 - 180 at 11 mm Hg
Density		Vapor Density	
Refractive Index		Vapor Pressure	
Evaporation Rate		Water Solubility	
Flash Point (°C)		EPA Code	
DOT Number		RTECS	
Comments			

More information about the chemical is available in these categories:

Physical Properties (3)

ABCR GmbH&Co KG

4-Phenoxyphenol, 99%

Environmental Science Center database with Experimental Log P coefficients etc.

Information about this particular compound

NIST Chemistry WebBook

Information about this particular compound

Patented May 18, 1948 2,441,576

UNITED STATES PATENT OFFICE

2,441,576

AMINO METHYL PHENOLS

Eldon M. Jones and Albert L. Rawlins, Grosse Pointe Woods, and Joseph H. Burckhalter and Walter F. Holcomb, Detroit, Mich., assignors to Parke, Davis & Company, Detroit, Mich., a corporation of Michigan

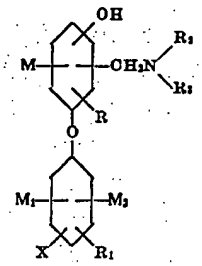
No Drawing. Application April 22, 1944, Serial No. 532,373

5 Claims. (Cl. 260—570.9)

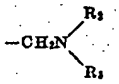
1

The invention relates to new phenolic diphenyl ethers containing at least one aminomethyl group attached directly to a benzene ring to which a phenolic hydroxyl is also attached. The invention also relates to processes for obtaining these new products.

The compounds of the invention have the general formula



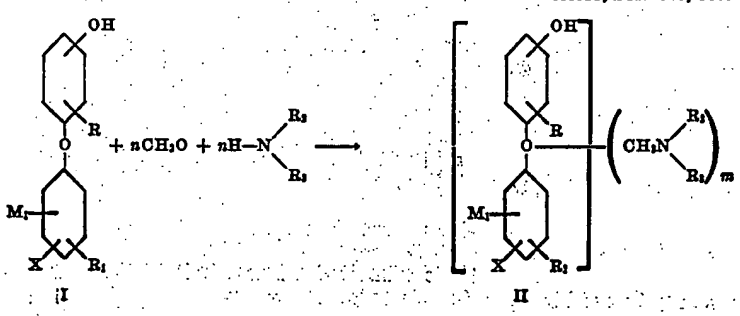
where M, M_1, and M_2 are members of the class H and



R and R_1 are members of the class H, alkylene, halogen and alkyl, R_2 is H, alkyl, alkylene or hydroxyalkyl containing not more than six carbon atoms, R_3 is alkyl, alkylene or hydroxyalkyl, containing not more than six carbon atoms and X is a member of the class hydrogen, halogen, and hydroxyl.

These compounds can be prepared by several methods.

A.—A phenolic diphenyl ether can be treated with formaldehyde and a non-aromatic amine to cause a transformation which may be represented as follows:



I II

2

where R, R_1, R_2, R_3, M_1, and X have the values already given under the general formula, and where *n* is one of the integers 1, 2, 3 or 4 and *m* is 1, 2, 3 or 4.

A variation of this procedure is to cause the formaldehyde and the secondary amine to react in a suitable solvent to form a dialkylaminomethanol or a dialkylaminomethyl alkyl ether, which may or may not be isolated before being treated with a phenolic diphenyl ether to give a product such as is illustrated by formula II.

B.—A phenolic diphenyl ether, illustrated by formula I, can be treated with formaldehyde and an alkaline catalyst, e. g., sodium hydroxide or potassium carbonate, to yield a methylol compound which can react with a primary or secondary amine in the presence of acid to give a substituted aminomethyl diphenyl ether such as is illustrated by formula II.

A variation of this process involves the treatment of the intermediate methylol compound in acetic acid with gaseous hydrogen chloride to form a chloromethyl derivative which may be isolated and treated with a suitable amine.

C.—The carbethoxy ester of a phenolic diphenyl ether, as described by formula I, may be chloromethylated by the procedure of Compt. rend., 197; 256 (1933). This chloromethyl derivative may be treated with an alcoholic solution of a primary or secondary amine and the intermediate thus formed hydrolyzed by refluxing with dilute alkali solution to give compounds represented by formula II above.

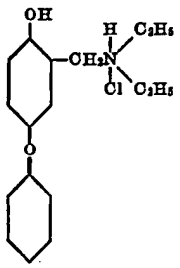
These new compounds are useful therapeutic agents, being characterized by their toxicity to bacteria and protozoa. Particularly, they are valuable as antimalarial agents and may be used in the form of their free bases or as salts of mineral acids, such as hydrochloric, hydrobromic, sulfuric, phosphoric, and sulfamic, or as salts of organic acids, such as acetic, propionic, lactic, citric, benzoic, etc.

These substances are also antioxidants and as such are useful as inhibitors.

In order to illustrate this invention the following examples are given, but they are not intended as limitations with respect to the phenols or the amines used or with respect to the conditions for reaction.

EXAMPLE I

Preparation of 2-diethylaminomethyl 4-phenoxyphenol hydrochloride

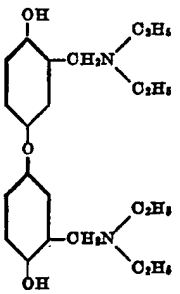


A mixture of 18.6 g. (0.10 mole) of 4-phenoxyphenol, 3.3 g. (0.11 mole) of paraformaldehyde, 8.0 g. (0.11 mole) of diethylamine, and 75 cc. of alcohol is heated in a steam bath for one hour. After most of the volatile material is removed by evaporation, the residue is treated with 50 cc. of concentrated hydrochloric acid and the resulting mixture is extracted with ether. The aqueous layer is separated and made alkaline with ammonia. The precipitated oil is extracted with ether and the extract washed with water and dried over anhydrous sodium sulfate. The ether is removed and the residue treated with an excess of alcoholic hydrogen chloride. Upon standing, a crystalline mass forms. This material is collected and washed with cold alcohol and dry ether; M. P. 161° C. Recrystallization from alcohol-ethyl acetate does not elevate the melting point.

EXAMPLE II

Preparation of 3,3'-bis(diethylaminomethyl)-4,4'-dihydroxyphenyl ether

To a solution of 10 g. (0.50 mole) of 4,4'-dihydroxyphenyl ether in 160 cc. of alcohol is added a solution of 35 g. (1.17 moles) of paraformaldehyde and 85 g. (1.17 moles) of diethylamine in 100 cc. of alcohol. The mixture is warmed in a steam bath in an open vessel for two hours. The desired product crystallizes upon cooling. After recrystallization from alcohol, the white crystalline material melts at 96–98° C. This compound which is the free base has the following formula:



The free base obtained as above may be readily converted into the desired salt by taking up in a suitable solvent and adding an acid as previously described such as hydrochloric, sulfamic, etc.

Instead of using 4,4'-dihydroxyphenyl ether as the starting material, the process may also be carried out with other dihydroxy diphenyl ethers in which the hydroxyl groups are substituted in the following positions 2,4'; 2,3'; 2,2'; 3,3'; 3,4' thereby obtaining in the form of the free base or its acid addition salts the following new compounds:

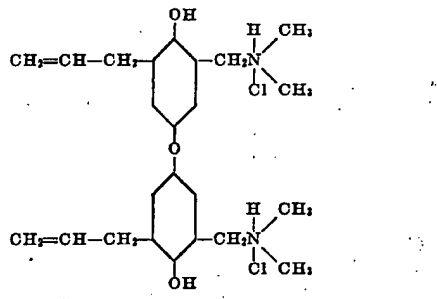
3,3' - bis (diethylaminomethyl) - 2,4'-dihydroxyphenyl ether
3,4' - bis (diethylaminomethyl) - 2,3'-dihydroxyphenyl ether
3,3' - bis (diethylaminomethyl) - 2,2'-dihydroxyphenyl ether
4,4' - bis (diethylaminomethyl) - 3,3'-dihydroxyphenyl ether
4,3' - bis (diethylaminomethyl) - 3,4'-dihydroxyphenyl ether

If other amines are used, e. g., dimethylamine, dipropylamine, dibutylamine, dihydroxyethylamine, ethylamine, hydroxyethylamine, the corresponding analogs of the above compounds may be obtained.

EXAMPLE III

Preparation of 3,3'-bis(dimethylaminomethyl)-4,4'-dihydroxy-5,5'-diallylphenyl ether dihydrochloride

To a solution of 8 g. of 3,3'-diallyl-4,4'-dihydroxyphenyl ether in 40 cc. of alcohol is added a solution of 2.6 g. of paraformaldehyde and 12.6 g. of 33% aqueous dimethylamine in 25 cc. of alcohol. The mixture is heated at refluxing temperature for one hour. After the solvent is removed, the residue is taken up in ether and treated with alcoholic hydrogen chloride. The precipitated crystalline dihydrochloride is collected and washed with dry ether; M. P. 238°. This compound has the formula:

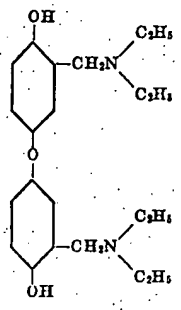


Instead of using a diallyl dihydroxy diphenyl ether as the starting material, other mono-alkyl or di-alkyl dihydroxy diphenyl ethers may also be used such for example as methyl, ethyl, propyl, butyl, amyl and hexyl dihydroxy diphenyl ethers thereby obtaining in the form of the free base or its acid addition salts analogous new compounds including, by way of example only, the following:

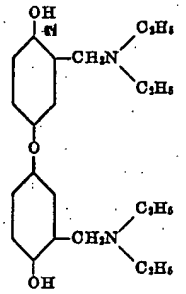
3,3' bis (dimethylaminomethyl)-4,4'-dihydroxy-5,5'-dimethylphenyl ether.
3,3' bis (dimethylaminomethyl) - 4,4'-dihydroxy-5,5'-diethylphenyl ether.

What we claim as our invention is:

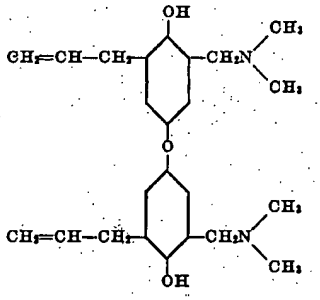
1. A compound of the class consisting of a free base and its acid addition salts, said free base having the following formula:



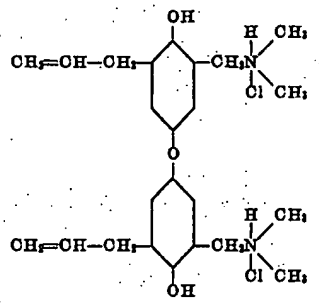
2. The compound having the formula:



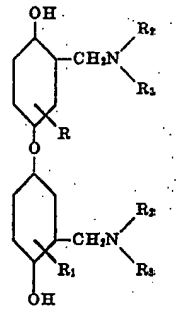
3. A compound of the class consisting of a free base and its acid addition salts, said free base having the following formula:



4. The compound having the formula:



5. A compound of the class consisting of a free base and its acid addition salts, said free base having the following formula:



where R and R_1 are the same members of the class consisting of hydrogen, alkyl, and alkenyl, both R_2 groups are the same member of the class consisting of hydrogen and alkyl containing not more than six carbon atoms, and R_3 is alkyl containing not more than six carbon atoms.

ELDON M. JONES.
ALBERT L. RAWLINS.
JOSEPH H. BURCKHALTER.
WALTER F. HOLCOMB.

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THE ACUTE TOXICITY OF PENTA-, HEXA-, AND HEPTACHLOROHYDROXYDIPHENYL ETHERS IN MICE

Terry L. Miller, David J. Lorusso,
Marilyn L. Walsh, Max L. Deinzer

Department of Agricultural Chemistry and Environmental Health Sciences Center, Oregon State University, Corvallis, Oregon

The acute intraperitoneal LD50 values of various hydroxychlorodiphenyl ethers (HO-Cl_x-DPEs; x = 5-7) in mice have been determined. The acute toxicities observed were on the order of, or slightly less than, that observed previously for 2-hydroxy-2',4,4'-trichlorodiphenyl ether (2-HO-Cl_3-DPE; Irgasan DP-300; Triclosan), a commonly used bactericide. However, the acute toxicities determined for these compounds were substantially less than have been observed for HO-Cl_9-DPEs and pentachlorophenol. The HO-Cl_x-DPEs had a marked hypothermic effect, similar to that produced by 2-HO-Cl_3-DPE. Symptomatology following exposure to the HO-Cl_x-DPEs (x = 5-7) suggested a nonspecific depressant effect on the central nervous system.

INTRODUCTION

Technical pentachlorophenol (PCP) is manufactured at a rate in excess of 50 million pounds per year in the United States alone (Arsenault, 1976), primarily for use in the wood and wood products industry. The process involved in the manufacture of PCP leads to production of a number of chlorinated impurities, principally (Firestone et al., 1972; Deinzer et al., 1978, 1979a, 1979b) the hydroxychlorodiphenyl ethers

This investigation was supported by grants from the National Institute of Environmental Health Sciences (individual research grant ES-01968, program project grant ES-00040, and center grant ES-00210).

The organization and analysis of the data base associated with this investigation were carried out in part using the PROPHET system, a unique national resource sponsored by National Institutes of Health. Information about PROPHET, including how to apply for access, can be obtained from the Director, Chemical/Biological Information-Handling Program, Division of Research Resources, National Institutes of Health, Bethesda, Maryland 20205.

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The authors wish to acknowledge Dr. Jo-Anne B. Campbell for the synthesis of some of the compounds used in the present work.

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(HO-Cl_x-DPEs; chlorinated phenoxyphenols; pre- and isopredioxins). The HO-Cl_x-DPEs are also known contaminants of other chlorophenols (Nilsson and Renberg, 1974), and are chlorodiphenyl ether metabolites (Tulp et al., 1979). Little is known about the toxicity and biological activity of these chemicals, even though the extensive and varied usage of technical PCP and other chlorophenols would seem to present a high potential for human exposure.

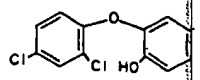
The acute toxicity values of the major HO-Cl_x-DPE contaminants in technical PCP have recently been investigated (Miller et al., 1982). Thus, 2-, 3-, and 4-HO-Cl_9-DPE have an acute intraperitoneal toxicity in mice approximately equal to or less than that of pure PCP. These compounds produce symptoms characteristic of those due to exposure to uncouplers of oxidative phosphorylation, including hyperthermia. The bactericide 2-hydroxy-2′,4,4′-trichlorodiphenyl ether (2-HO-Cl_3-DPE; Irgasan DP-300; Triclosan) has an acute ip LD50 24 h value of 184 (158–215) mg/kg (Miller et al., 1982), although the acute intravenous LD50 is 29 mg/kg and the acute oral LD50 is about 5000 mg/kg (Lyman and Furia, 1969). This compound also causes liver enlargement at a dose of 25 mg/kg (Kimbrough, 1974). In addition to their acute toxicity, the HO-Cl_9-DPEs have been shown to be markedly active toward biological membranes (Regös and Hitz, 1974; Miller and Deinzer, 1980; Lorusso et al., 1981a) and to affect rat liver microsomal mixed-function oxidase activity (Arrhenius et al., 1977; Miller et al., 1981; Lorusso et al., 1981b), as previously discussed (Miller et al., 1982).

This paper summarizes results of experiments on the acute intraperitoneal toxicity of a series of HO-Cl_x-DPEs with intermediate degree of chlorination ($x = 5$–7). Comparison is made to the toxicity of the HO-Cl_9-DPEs and 2-HO-Cl_3-DPE (Miller et al., 1982).

MATERIALS AND METHODS

Chemicals

The structures of the chemicals used in this study are shown in Fig. 1. 2-Hydroxy-2′,3′,4′,5′,6′-, 3-hydroxy-2′,3′,4′,5′,6′-, 4-hydroxy-2′,3′,4′,5′,6′-, and 2-hydroxy-2′,3,4,4′,5-pentachlorodiphenyl ether (respectively called 2-HO-2′,3′,4′,5′,6′-, 3-HO-2′,3′,4′,5′,6′-, 4-HO-2′,3′,4′,5′,6′-, and 2-HO-2′,3,4,4′,5-Cl_5-DPE), and 2-hydroxy-2′,3′,4,5,5′,6′-hexachlorodiphenyl ether (2-HO-2′,3′,4,5,5′,6′-Cl_6-DPE) and 2-hydroxy-2′,3′,4,4′,5,5′,6′-heptachlorodiphenyl ether (2-HO-2′,3′,4,4′,5,5′,6′-Cl_7-DPE) were synthesized as described by Kolonko et al. (1981). 2-Hydroxy-2′,4,4′,5,5′-pentachlorodiphenyl ether (2-HO-2′,4,4′,5,5′-Cl_5-DPE; pre-2,3,7,8-tetrachlorodibenzo-*p*-dioxin; pre-TCDD) was synthesized using the crown ether-catalyzed coupling step described by Kolonko et al. (1981), followed by the synthetic reaction sequence described by Nilsson and Anderson (1977).



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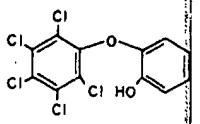
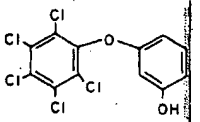
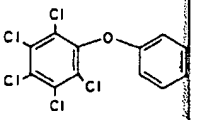


2-HO-2′,3′,4′,5′,6′-Cl_5



3-HO-2′,3′,4′,5′,6′-Cl_5



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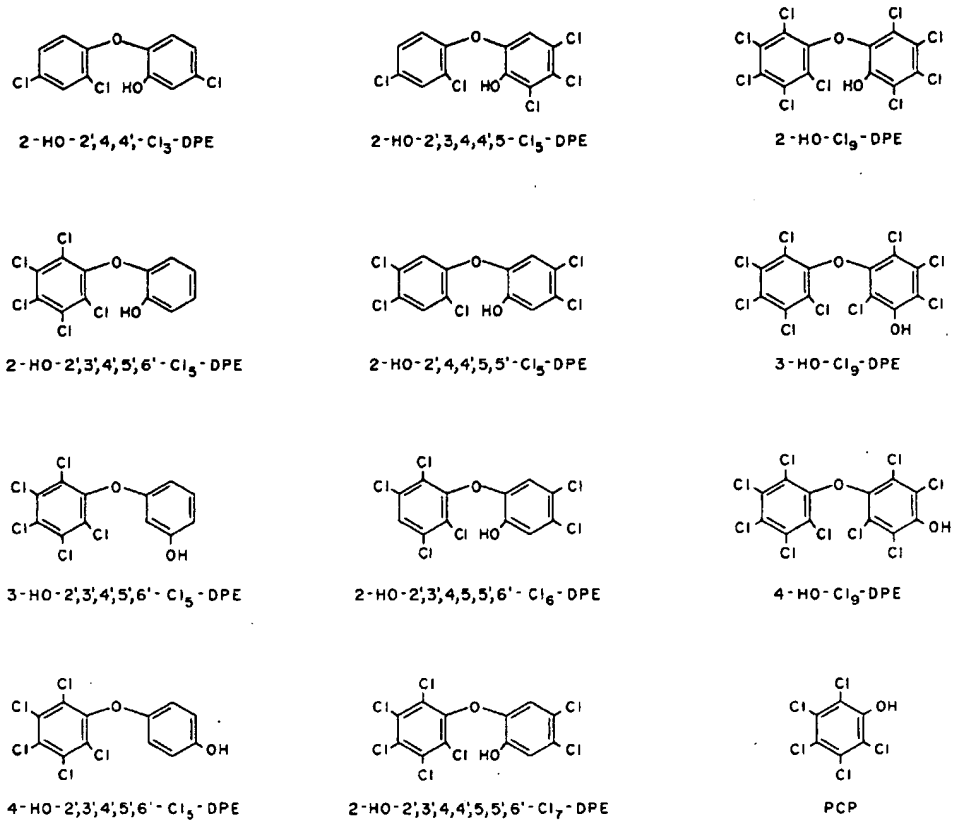

FIGURE 1. Structures of hydroxychlorodiphenyl ethers.

Each of these products was further purified by reverse-phase high-performance liquid chromatography (HPLC) on 25–40 μm Lichroprep RP-18 (MCB Manufacturing Chemists, Inc.: Cincinnati, Ohio). The final products were of greater than 99% purity and contained less than 1 ppm of chlorinated dibenzo-*p*-dioxin as estimated by a combination of HPLC and electron capture gas chromatographic techniques. All other hydroxychlorodiphenyl ethers used in this study were synthesized and purified as previously described (Miller et al., 1982).

Animals

Female, albino CD-1 mice were obtained from Charles River Laboratories, Wilmington, Mass. The animals (4–6 wk old, 23–26 g) were housed over corn-cob bedding in a room with controlled temperature (24–27°C) and photoperiod, and were allowed food and water *ad libitum* before and during the experiments. The control and experimental groups consisted of six mice each; each group was housed in a separate cage. Mice were

ear-tagged and assigned to each group of six by a randomization technique (Goldstein, 1964).

Acute Toxicity

After being weighed, the animals were dosed with each of the compounds by intraperitoneal (ip) injection, with pure DMSO as the vehicle. The geometric dose factor used for each compound is given in Table 1. Both experimental and control animals received DMSO at a dose of 50 μl/20 g body weight. Mice were observed for 3–6 h immediately following dosing and then daily for at least 3 wk. Weights were recorded periodically during the first 3 wk. The median lethal dose based upon deaths during the first 24 h (LD50–24 h) was calculated by the tabular method of Weil (1952) and the graphical method of Litchfield and Wilcoxin (1949). Application of the latter method also yielded the potency ratio and its 95% confidence limits, where permitted by the data.

Rectal Temperature Measurements

Experiments were performed at an ambient temperature of 23–27°C. Mice were placed in the temperature-controlled environment 1 h before commencement, and maintained there for the duration of the experiment. The animals were given an LD50 dose as described above, with each experimental group consisting of the indicated number of mice. Rectal

TABLE 1. Acute Toxicity[a] of Hydroxychlorodiphenyl Ethers (HO-Cl_x-DPEs) in Mice

Compound	LD50[b,c] μmol/kg	LD50[b,c] mg/kg	Potency ratio[c]
2-HO-2',3',4,4',5,5',6'-Cl_7-DPE	590 (440–791)[e]	252 (188–338)[e]	1.8 (1.3–2.5)[e]
2-HO-2',3',4,5,5',6'-Cl_6-DPE	361 (290–445)[d]	142 (114–175)[d]	1.0 (0.8–1.3)[d]
2-HO-2',4,4',5,5'-Cl_5-DPE	396 (290–445)[d]	142 (118–170)[d]	1.0[d]
2-HO-2',3,4,4',5-Cl_5-DPE	474 (365–617)[d]	170 (131–221)[d]	1.2 (0.9–1.7)[d]
2-HO-2',3',4',5',6'-Cl_5-DPE	>1674[g]	>600[g]	–[f]
3-HO-2',3',4',5',6'-Cl_5-DPE	474 (226–990)[f]	170 (81–355)[f]	–[f]
4-HO-2',3',4',5',6'-Cl_5-DPE	>2510[g]	>900[g]	–

[a] 24 h acute intraperitoneal toxicity; DMSO used as vehicle (50 μl/20 g body weight); animal weight = 26.3 ± 3.2 g ($n = 318$).

[b] The geometric dose factors used are: 2-HO-2',3',4,4',5,5',6'-Cl_7-DPE and 4-HO-2',3',4',5',6'-Cl_5-DPE, 2; 2-HO-2',3,4,4',5-Cl_5-DPE, 1.5; 2-HO-2',3',4',5',6'-Cl_5-DPE, 1.4; 2-HO-2',4,4',5,5'-Cl_5-DPE and 3-HO-2'3',4',5',6'-Cl_5-DPE, 1.3; 2-HO-2',3',4,5,5',6'-Cl_6-DPE, 1.2.

[c] Calculated by the graphical method of Litchfield and Wilcoxin (1949); based on data from one or more experiments.

[d,e] Values with the same superscript are statistically indistinguishable; values with different superscripts are significantly different ($p < 0.05$); determined by the method of Litchfield and Wilcoxin (1949); based on potency ratio.

[f] Log dose-response curve not parallel to 2-HO-2',4,4',5,5'-Cl_5-DPE.

[g] Value corresponds to highest dose used.

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PEs) in Mice

	Potency ratio[c]
338)[e]	1.8 (1.3–2.5)[e]
175)[d]	1.0 (0.8–1.3)[d]
170)[d]	1.0[d]
221)[d]	1.2 (0.9–1.7)[d]
355)[f]	—[f]
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temperatures were measured using a YSI Model 42SC Telethermometer (Yellow Springs Instruments, Yellow Springs, Ohio) with a YSI423 probe lubricated with petroleum jelly and inserted to a constant depth of 1 cm into the rectum of the mouse.

RESULTS

The acute toxicity of the HO-Cl_x-DPEs studied here was substantially less than that observed earlier for the HO-Cl_9-DPEs (Miller et al., 1982), when compared at the LD50 (Table 1). Results obtained by the method of Weil (1952) and of Litchfield and Wilcoxin (1949) were statistically indistinguishable; values obtained by the graphical method of Litchfield and Wilcoxin are presented in Table 1. Analysis by this method indicated that the log dose-probit curves were statistically parallel at the 95% confidence level for all of the compounds except 3-HO-2',3',4',5',6'-Cl_5-DPE; it was therefore possible to calculate the potency ratio of one compound relative to another (except 3-HO-2',3',4',5',6'-Cl_5-DPE). Table 1 shows the potency ratio as obtained from data from one or more determinations of LD50–24 h values. On the basis of potency ratios and LD50 values, the relative acute toxicity of the intermediate HO-Cl_x-DPEs is in the following order: pre-TCDD $\simeq$ 2-HO-2',3',4,5,5',6'-Cl_6-DPE $\simeq$ 2-HO-2',3,4,4',5-Cl_5-DPE $\simeq$ 3-HO-2',3',4',5',6'-Cl_5-DPE (valid only at the LD50) $>$ 2-HO-2',3',4,4',5,5',6'-Cl_7-DPE $\gg$ 2-HO-2',3',4',5',6'-Cl_5-DPE $\simeq$ 4-HO-2',3',4',5',6'-Cl_5-DPE. The response of each sample of mice to each compound tested was reasonably homogenous as judged by the relatively small standard deviation (0.1–0.29), except for 3-HO-2',3',4',5',6'-Cl_5-DPE for which the standard deviation was 0.7. The latter compound will show significant acute toxicity at doses below which the other HO-Cl_x-DPEs would show little or none.

Unlike the results obtained with HO-Cl_9-DPEs (Miller et al., 1982), where all deaths occurred within the initial 24 h observation period, the HO-Cl_x-DPEs used in this study continued to cause death over a longer period of time (up to 4 d in most cases). Thus, for some of the compounds, it was possible to determine an LD50 at 4 d (LD50–4 d) by using data from the same groups of animals used for determination of the LD50–24 h. The LD50–4 d so determined were as follows: 2-HO-2',3',4,4',5,5',6'-Cl_7-DPE, 166 (124–221) mg/kg; 2-HO-2',3,4,4',5-Cl_5-DPE, 41 (18–92) mg/kg; and 3-HO-2',3',4',5',6'-Cl_5-DPE, 106 (5–206) mg/kg. Data obtained from animals exposed to the other HO-Cl_x-DPEs was too incomplete to permit analysis by the method of Litchfield and Wilcoxin (1949), and insufficient quantities of the chemicals were available for an independent determination of LD50–4 d. As to be expected, the LD50–4 d in each case was lower than the LD50–24 h value. Because of the possibility for its conversion to TCDD, animals exposed to pre-TCDD in a separate experiment were studied in more detail; a 3-wk LD50 value of 57 (47–70) mg/kg was obtained for this predioxin.

The HO-Cl_x-DPEs ($x = 5$–7) used in this study produced symptomatology preceding death that was much different than that observed (Miller et al., 1982) for the higher chlorinated HO-Cl_9-DPEs, but that was very similar to that observed for animals exposed to 2-HO-Cl_3-DPE. Each of the compounds studied produced similar symptomatology, which included general lethargy, lassitude, close huddling, almost complete lack of response to tactile stimuli, piloerection, and no apparent increase in respiratory rate and no hyperactivity. The animals felt cool to the touch. None of the above symptoms were observed in animals treated with DMSO alone. Surviving animals were observed for a minimum of 3 wk, during which time no significant weight loss was detected for pre-TCDD or any other pre- or isopredioxin studied.

Pure PCP, 2-, 3-, and 4-HO-Cl_9-DPE each caused slight hyperthermia (Fig. 2) in mice maintained at approximately 25°C, although the response to a given dose was somewhat variable from mouse to mouse. This hyperthermic effect was less than previously observed at 32°C (Miller et al., 1982) for the same compounds. The other HO-Cl_x-DPEs tested all demonstrated hypothermic effects (Fig. 2) similar to that observed with 2-HO-Cl_3-DPE (Miller et al., 1982). The efficacy of the HO-Cl_x-DPEs at inducing temperature depression is estimated to be in the following order: 2-HO-Cl_3-DPE > 2-HO-2′,3′,4,5,5′,6′-Cl_6-DPE ≃ pre-TCDD ≃ 2-HO-2′,3′,4,4′,5,5′,6′-Cl_7-DPE > 2HO-2′,3,4,4′,5-Cl_5-DPE > 2-HO-2′,3′,4′,5′,6′-Cl_5-DPE > 4-HO-2′,3′,4′,5′,6′-Cl_5-DPE.

DISCUSSION

Previous work from our laboratory has shown that the higher chlorinated HO-Cl_x-DPEs ($x = 9$) display significant acute ip toxicity in mice. Based on work reported herein, HO-Cl_x-DPEs of intermediate degree of chlorination ($x = 5$–7) are also toxic to mice following ip administration. Because the log dose-probit curves for the HO-Cl_x-DPEs ($x = 5$–7) are not parallel to response curves for the HO-Cl_9-DPEs, it was not possible to calculate the potency ratio for use as a measure of relative acute toxicity of the HO-Cl_x-DPEs ($x = 5$–7) and HO-Cl_9-DPEs (Litchfield and Wilcoxin, 1949). It is possible, however, to compare the acute toxicity at a specified portion of the dose-probit curve, e.g., at the LD50 (Goldstein et al., 1974). Using the LD50, then, as a basis for comparison of acute toxicity, the present data can be integrated with that obtained by Miller et al. (1982) to give the following order for the relative acute toxicity of the HO-Cl_x-DPEs: 2-HO-Cl_9-DPE > 3-HO-Cl_9-DPE > 4-HO-Cl_9-DPE ≃ pre-TCDD ≃ 2-HO-2′,3′4,5,5′,6′-Cl_6-DPE ≃ 2-HO-2′,3,4,4′,5-Cl_5-DPE ≃ 3-HO-2′,3′,4′,5′,6′-Cl_5-DPE ≃ 2-HO-Cl_3-DPE > 2-HO-2′,3′,4,4′,5,5′,6′-Cl_7-DPE ≫ 2-HO-2′,3′,4′,5′,6′-Cl_5-DPE ≃ 4-HO-2′,3′,4′,5′,6′-Cl_5-DPE. It must be emphasized that this comparison is valid only at doses corresponding to the LD50 and is not meant to be an expression of relative potency in

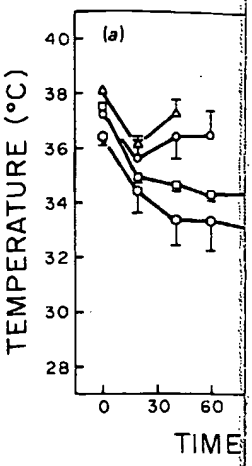

FIGURE 2. Effect
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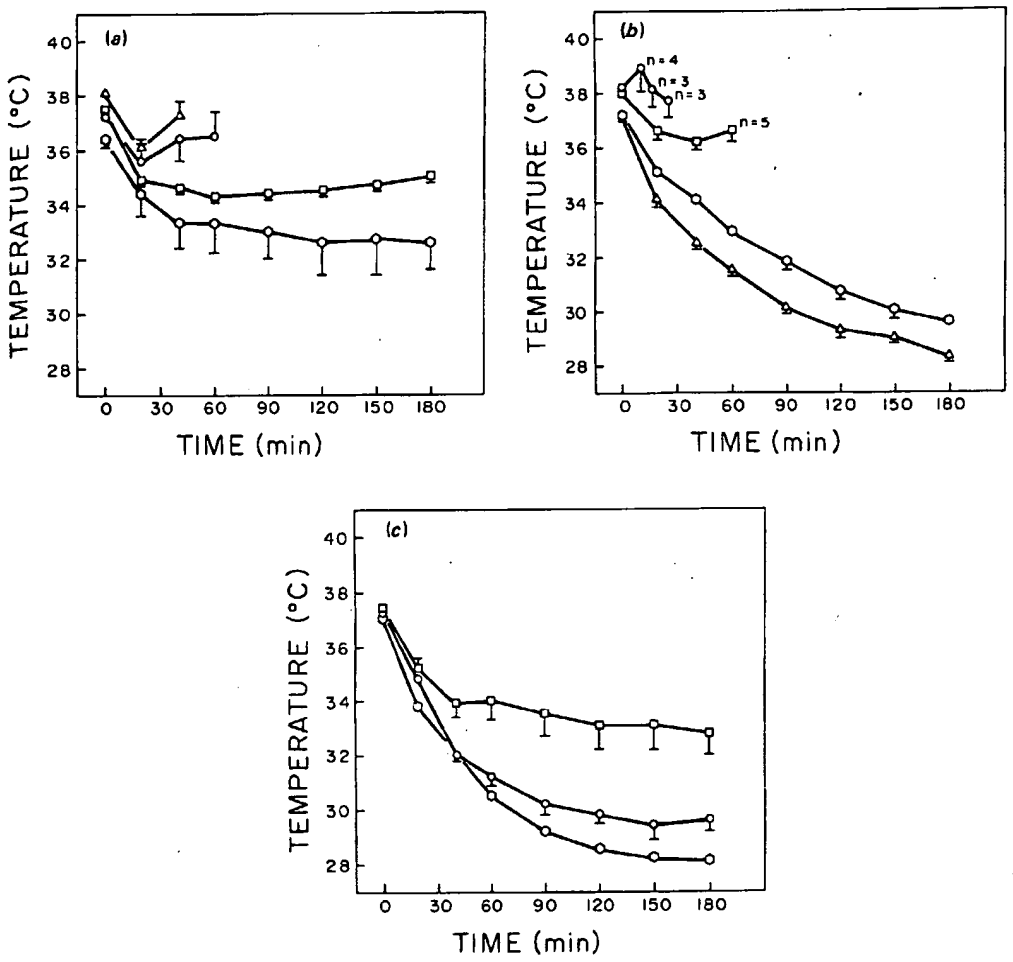

FIGURE 2. Effect of HO-Cl_x-DPEs on mean body temperature (±SE) of mice maintained at approximately 23–27°C. (*a*) □ DMSO, 2.5 ml/kg; ○ 2-HO-Cl_9-DPE, 47 mg/kg; △ 3-HO-Cl_9-DPE, 89 mg/kg; ○ 2-HO-2',3',4',5',6'-Cl_5-DPE, 600 mg/kg; (*b*) ○ Pure PCP, 58 mg/kg; □ 4-HO-Cl_9-DPE, 132 mg/kg; ○ 2-HO-2',3,4,4',5-Cl_5-DPE, 170 mg/kg; △ 2-HO-2',4,4',5,5'-Cl_5-DPE, 135 mg/kg; (*c*) □ 4-HO-2',3',4',5',6'-Cl_5-DPE, 900 mg/kg; ○ 2-HO-2',3',4,4',5,5',6'-Cl_7-DPE, 252 mg/kg; ○ 2-HO-2',3',4,5,5',6'-Cl_6-DPE, 142 mg/kg. Each point represents data obtained with 6 mice ($n = 6$), except for 2-HO-2',3',4',5',6'-Cl_5-DPE where $n = 3$ and DMSO where $n = 18$ (except where indicated otherwise). When animals died during the course of the experiment, the number of animals remaining is indicated by *n*. Where none is indicated, the value of the SE is within the dimension of the symbol.

general. The basis for the differences in toxicity is not obvious, although the nonachlorocompounds are more toxic than the HO-Cl_x-DPEs of lower degree of chlorination.

Each of the HO-Cl_x-DPEs studied here, as well as 2-HO-Cl_3-DPE (Miller et al., 1982), cause death over a period of at least 4 d. On the other hand, all animals exposed to the nonachloro compounds (HO-

Cl_9-DPEs) die within 24 h after dosing, and evidence has been presented that suggests that the HO-Cl_9-DPEs cause death by uncoupling oxidative phosphorylation (Miller et al., 1982). The time response to death and the hypothermia observed here indicates that the cause of death following exposure to the HO-Cl_x-DPEs of intermediate degree of chlorination ($x = 5–7$) is probably by a mechanism unrelated to uncoupling of oxidative phosphorylation. It is instead more typical of an encephalopathic effect, as described by Boyd (1972). Thus the observed prolonged general lethargy, lack of response to tactile stimuli, lassitude, weakness, hypothermia, and passive nature are suggestive of a suppressive effect on the central nervous system.

The hypothermia observed for the intermediate HO-Cl_x-DPEs ($x = 5–7$) is in contrast to the slight, but significant, hyperthermia observed with the HO-Cl_9-DPEs. Calculation of the difference in mean temperature between experimentals and controls at a specified time after dosing allowed for the correlation of this difference with the number of chlorine atoms on the HO-Cl_x-DPE. Values for the HO-Cl_9-DPEs were calculated only at 40 min, since no mice survived longer than 60 min; for these compounds this was considered to be the time of maximum temperature response. A positive correlation coefficient was found both at 40 min ($r = 0.81$; $t = 3.9$) and at 180 min ($r = 0.83$; $t = 4.2$) after ip injection; the mean temperature difference at the latter time was the maximum response for the HO-Cl_x-DPEs ($x = 5–7$) and 2-HO-Cl_3-DPE. Since the calculated t-value for each correlation coefficient was greater than the critical t-value, there was a significant correlation between depression of body temperature and a decrease in the number of chlorine atoms on the HO-Cl_x-DPE. The significance of this correlation is not readily apparent.

In addition to their acute toxicity, recent results from our laboratory show that some HO-Cl_x-DPEs are potent inducers of the hepatic MFO system (Miller et al., 1981; Lorusso et al., 1981b). A complete assessment of the health effects associated with environmental exposure to these chemicals must await the results of further experimentation.

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Antiplasmodial and Cytotoxic Activity of Natural Bisbenzylisoquinoline Alkaloids

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As part of an ongoing collaborative effort to discover new antimalarial agents from natural sources, we have tested 53 bisbenzylisoquinoline alkaloids for cytotoxicity against cultured mammalian cells and for antiplasmodial activity against chloroquine-sensitive and chloroquine-resistant clones of *Plasmodium falciparum*. The isolates from *Cyclea barbata*, *Stephania pierrei*, *Stephania erecta*, *Pachygone dasycarpa*, *Cyclea atjehensis*, *Hernandia peltata*, *Curare candicans*, *Albertisia papuana*, and *Berberis valdiviana* exhibited a wide range of biological potencies in antiplasmodial assays, and the majority exhibited some degree of cytotoxicity against human KB cells. More than half of the compounds tested, however, showed selective antiplasmodial activity, with >100-fold greater toxicity toward one or both of the *P. falciparum* clones, relative to cultured mammalian cells. The most selective alkaloids were (−)-cycleanine (**40**), (+)-cycleatjehine (**50**), (+)-cycleatjehenine (**49**), (+)-malekulatine (**3**), (−)-repandine (**13**), and (+)-temuconine (**2**). As a result of these studies, relationships between the structures, the stereochemistry, and the substitution patterns of these alkaloids and their in vitro antiplasmodial and cytotoxic activities are beginning to emerge.

Bisbenzylisoquinolines are a large and diverse group of natural alkaloids that occur in many plant species, particularly in members of the Menispermaceae, Berberidaceae, Ranunculaceae, Annonaceae, and Monimiaceae.[1−4] Many of the plants that contain these compounds enjoy a folkloric reputation as medicinals in various cultures.[1−4] Recently, bisbenzylisoquinoline alkaloids have been widely demonstrated to possess a number of interesting and potent biological activities, including cytotoxicity and/or antiplasmodial activity.[1−4] Classically, these dimers can be divided into three categories: biscoclaurines, coclaurine−reticulines, and bisreticulines. The two moieties are usually bound by one diaryl ether bridge or more, although carbon−carbon bridges or a methylene−oxy bridge may be present. The bisbenzylisoquinoline alkaloids are classified according to the nature, the number, and the attachment point of the bridges. In each subgroup, the alkaloids differ by the nature of their oxygenated substituents, the degree of unsaturation of the heterocyclic rings, and the stereochemistry of their two chiral centers, C-1 and C-1′. The diversity of pharmacological effects observed within this group of molecules is obviously a function of differences in chemical structures; however, convincing structure−activity relationships had not been developed previously for the bisbenzylisoquinoline alkaloids.

Over the past several years, we have explored this class of complex alkaloids in considerable spectroscopic detail, as well as evaluating their biologic potential to serve as new antimalarial agents. Through bioassay-directed fractionation, we have isolated a variety of known and novel bisbenzylisoquinoline alkaloids from several plants in the Menispermaceae, including *Stephania erecta*,[5] *Stephania pierrei*,[6] *Cyclea barbata*,[7−9] and *Pachygone dasycarpa*.[10] In addition, a number of bisbenzylisoquinoline alkaloids that had been isolated in the course of phytochemical studies of other species, such as *Cyclea atjehensis*[11,12] (Guinaudeau and Ovono, unpublished result), *Curare candicans*,[13] *Cocculus pendulus* (Menispermaceae),[14] *Hernandia peltata* (Hernandiaceae),[15] and *Berberis valdiviana* (Berberidaceae)[16] were available for investigation. Applying identical methodologies, these compounds have been analyzed for cytotoxicity toward mammalian cells, as well as for antiplasmodial activity with chloroquine-sensitive and chloroquine-resistant, mefloquine-sensitive clones of *Plasmodium falciparum*. This approach is used to determine antimalarial potency as well as selectivity. Compilation of the results obtained with 53 bisbenzylisoquinoline alkaloids has facilitated the analysis of structure−activity relationships wherein the goal is to define the structural features that might be responsible for selective antiplasmodial activity.

Results and Discussion

Of the bisbenzylisoquinoline alkaloids examined in this study (**1**−**53**), only three, (−)-isocuricycleatjine (**45**), (−)-dehydroisocuricycleatjenine (**47**), and (+)-tubocurarine chloride (**48**) failed to show significant in vitro antiplasmodial activity against either of the *P. falciparum* clones tested (Table 1). Seven additional compounds (**15**, **19**, **38**, **43**, **44**, **46**, **53**) exhibited weak activity, with antiplasmodial IC_{50} values of 1000−2400 nM in at least one of the clones. The remaining 43 compounds were determined to have IC_{50} values of <1000 nM against both D6 and W2 clones, and of these, 27 demonstrated potent activity of <200 nM with at least one of the clones. To further analyze the antimalarial potential of these bisbenzylisoquinoline alkaloids, all compounds were evaluated for cytotoxicity with human epidermoid carcinoma (KB) cells.

Many compounds have been reported in the literature as "antimalarials" on the basis of in vitro data against malarial parasites. Although completely valid, these data

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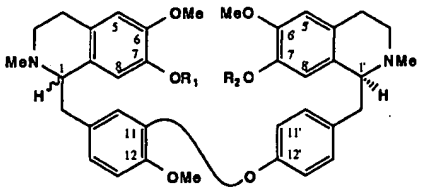
Table 1. Cytotoxic and Antiplasmodial Activity of Selected Bisbenzylisoquinolines

compound no.	bisbenzylisoquinoline name/code	KB ED_{50}[a]	D6 IC_{50}[a]	D6 SI[b]	W2 IC_{50}[a]	W2 SI[b]
1	(+)-neothalibrine	10 100	47	215	135	75
2	(+)-temuconine	>32 100	213	>150	227	>140
3	(+)-malekulatine	>29 900	61	>490	164	>180
4	(−)-cycleapeltine[d]	3620	48	76	67	54
5	(+)-limacusine	4110	64	64	192	21
6	(+)-homoaromoline	10 400	173	60	474	22
7	(+)-obaberine[c]	13 800	371	37	347	40
8	(+)-stephibaberine[c]	10 500	214	49	510	21
9	(+)-daphnandrine[c]	9800	106	92	375	26
10	(+)-2-norobaberine[c]	9900	75	130	154	64
11	(+)-2-norcepharanthine[c]	6600	79	84	219	30
12	(+)-cepharanthine[c]	9700	231	42	478	20
13	(−)-repandine	15 000	42	350	67	220
14	(+)-candicusine	8600	29	300	105	82
15	(+)-aromoline	14 800	446	33	1400	11
16	(+)-tetrandrine[d]	5800	288	20	257	22
17	(−)-pheanthine	10 800	305	35	498	22
18	(+)-isotetrandrine[c]	10 600	260	40	88	120
19	(+)-tetrandrine 2′-*N*-oxide	>31 300	1980	>16	948	>34
20	(+)-fangchinoline	9210	179	51	306	30
21	(−)-limacine[d]	16 100	86	186	263	61
22	(+)-thalrugosine[c]	10 700	199	54	378	28
23	(+)-berbamine	9210	128	72	313	29
24	(+)-atherospermoline	3700	232	16	623	6
25	(+)-obamegine	14 100	354	40	825	17
26	(+)-*N*-methyl-7-*O*-desmethylpeinamine	17 500	134	130	609	29
27	(+)-2-norberbamine	7100	47	149	193	36
28	(+)-2-norisotetrandrine[c]	10 100	106	95	728	140
29	(+)-2-northalrugosine[c]	10 400	115	92	210	50
30	(−)-2′-norlimacine	2700	118	23	218	12
31	(+)-tricordatine	4900	90	55	259	19
32	(+)-isotrilobine	24 000	388	62	788	30
33	(+)-12-*O*-methyltricordatine	6000	30	200	112	54
34	(+)-cocsuline	10 000	87	110	502	7
35	(+)-2′-norcocsuline	3800	48	79	281	14
36	(+)-*N*-methyltelobine[c]	8300	169	49	451	19
37	(+)-1,2-dehydrotelobine[c]	5000	554	11	464	11
38	(−)-6,12-*O*-desmethylthalmine	17 800	883	20	1590	11
39	(+)-thalmirabine	8400	224	37.7	110	76.4
40	(−)-cycleanine	>33 700	73	>460	247	>140
41	(−)-curine	7700	128	60	387	20
42	(+)-2′-norcuricycline	14 400	530	27.1	676	21.2
43	(+)-2′-norisocuricycline	8800	1270	7.5	662	13.3
44	(−)-curicycleatjenine	8360	2320	3.6	1200	7.0
45	(−)-isocuricycleatjine	8870	6890	1.3	4030	2.2
46	(−)-isocuricycleatjenine	13 600	1910	1.6	1050	13
47	(−)-isocuricycleatjehimine	>33 900	4980	>6.8	2100	>16.1
48	(+)-tubocurarine chloride	>32 800	15300	>2.1	>16 400	ca. 2
49	(+)-cycleatjehenine	14 700	115	130	66	220
50	(+)-cycleatjehine	>33 900	110	>310	59	>580
51	(+)-3′,4′-dihydrocycleatjehenine	>33 800	346	>98	169	>200
52	(+)-2′-noratjecycline	8580	348	24.6	199	43.2
53	(−)-*N*-acetyl-2′-noratjecycline	20 600	1030	20	605	34
	antimalarial standard drugs (n = 12)	KB ED_{50}[a]	D6 IC_{50}[a]	D6 SI[b]	W2 IC_{50}[a]	W2 SI[b]
	chloroquine	33700	6.18 ± 0.71	5460	135 + 10	250
	quinine	>55 400	23.38 ± 7.04	>285	250 + 16.2	>222
	mefloquine	8430	18.12 ± 1.52	465	7.78 + 0.51	1080
	artemisinin	>70 900	15.14 ± 0.26	>4680	14.60 + 2.02	>4860

[a] IC_{50} and ED_{50}values are expressed in nM. [b] Selectivity index (SI) is defined as the ratio of cytotoxicity over antiplasmodial activity. [c] Data previously published in Likhitwitayawuid et al.[5] [d] Data previously published in Lin et al.[7]

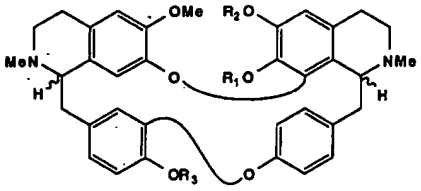
can be somewhat misleading. Most general cytotoxins can be legitimately called "antiplasmodial" under conditions of in vitro testing. As an attempt to establish a working model system to estimate the potential of test compounds such as bisbenzylisoquinolines for inhibiting the growth of an intra-erythrocytic malaria parasite without host toxicity, we have defined the in vitro selectivity index (SI) of a test substance as ED_{50} (in KB cells) /IC_{50} (in *P. falciparum*).[8] KB cells (human oral epidermoid carcinoma) were selected in part by precedent[17] and also because, in our experience, this line exhibits an intermediate sensitivity to a large number of cytotoxic agents when compared to cell lines derived from a variety of other human tumors (unpublished observations). Because the in vivo therapeutic index of a drug encompasses a much broader spectrum of toxic effects than would be reflected in the SI, it would be inappropriate

Chart 1



1 : 1*S* , 1'*S*; R_1=H; R_2=Me

2 : 1*R* , 1'*S*; R_1=Me; R_2=H



4 : 1*S* , 1'*S*; R_1=H; R_2=Me; R_3=Me

5 : 1*R* , 1'*R*; R_1=H; R_2=Me; R_3=Me

6 : 1*R* , 1'*S*; R_1=H; R_2=Me; R_3=Me

7 : 1*R* , 1'*S*; R_1=Me; R_2=Me; R_3=Me

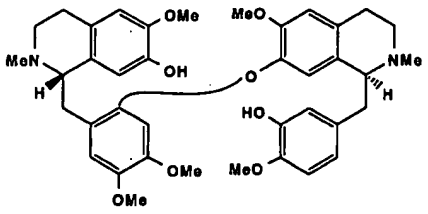
8 : 1*R* , 1'*S*; R_1=Me; R_2=H; R_3=Me

12 : 1*R* , 1'*S*; R_1-R_2=CH_2; R_3=Me

13 : 1*S* , 1'*S*; R_1=Me; R_2=Me; R_3=H

14 : 1*R* , 1'*R*; R_1=H; R_2=Me; R_3=H

15: 1*R* , 1'*S*; R_1=H; R_2=Me; R_3=H



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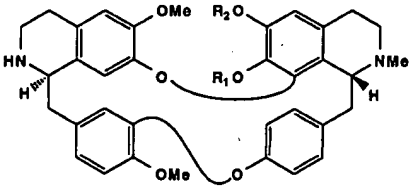


9 : R_1=H; R_2=Me

10 : R_1=Me; R_2=Me

11 : R_1-R_2=CH_2

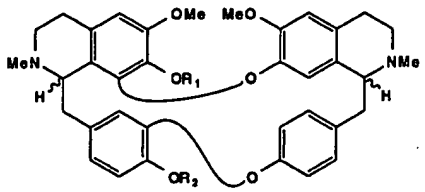
to speculate on the clinical significance of SI values. Nonetheless, this does not diminish the utility of the SI parameter in guiding bioactivity-directed fractionation and prioritizing the further evaluation of compounds/extracts exhibiting in vitro antiplasmodial activity. The SIs of a number of the bisbenzylisoquinolines reported here compare favorably to those of quinine, chloroquine, and mefloquine, which have been included as controls.

Among the 53 alkaloids tested for toxicity toward cultured *P. falciparum* and mammalian KB cells, **1**−**3** contain only one etheroxy bridge (Chart 1). Each exhibited an impressive SI of well over 100, with the exception of (+)-neothalibrine (**1**) in the W2 clone. The structural differences between (1*S*,1'*S*)-(+)-neothalibrine and (1*R*,1'*S*)-(+)-temuconine (**2**) are the different substituents at C-7 and C-7' and that the configuration at C-1 is *S* for the former alkaloid and *R* for the latter. The effect of these differences on the activity can be related to the toxicity; the threefold enhancement of activity observed for the *S* enantiomer is parallel to the change in cytotoxicity, with the result that the SI values of (+)-neothalibrine (**1**) are not notably different from those for (+)-temuconine (**2**). The lack of detectable toxiçity in (+)-temuconine (**2**) is a rare characteristic among the bisbenzylisoquinoline alkaloids that we[5,7] and others[1−4] have assayed. Lack of toxicity is also observed with (+)-malekulatine (**3**). It is interesting to note that (+)-malekulatine (**3**) belongs to a different class of bisbenzylisoquinoline, being a bisreticuline derivative and not a biscoclaurine, as are (+)-temuconine (**2**) and all of the other compounds in Table 1. Moreover, (+)-malekulatine (**3**) is a head-to-tail dimer, whereas (+)-neothalibrine (**1**) and (+)-temuconine (**2**) are linked tail-to-tail, although in each case, the two benzylisoquinoline moieties are linked by only one etheroxy bridge. This structural characteristic allows these three compounds to assume a relatively linear conformation, as shown by NOE experiments.[15,16]

Twenty-seven dimers, half of the compounds we have subjected to bioassay evaluation, belong to the two most prevalent subgroups of bisbenzylisoquinoline alkaloids, in which the two benzylisoquinoline moieties are linked by two etheroxy bridges either between C-7,C-8' and C-11,C-12', or between C-8,C-7' and C-11,C-12'. Twelve alkaloids possessing the former type of linkage were evaluated, of which only three presented appreciable selectivity for malarial parasites: (−)-repandine (**13**), (+)-candicusine (**14**), and (+)-2-norobaberine (**10**).

(1*S*,1'*S*)-(−)-Cycleapeltine (**4**) and (1*R*,1'*R*)-(+)-limacusine (**5**), mirror images of each other, exhibit good antiplasmodial activity against both clones of *Plasmodium*, but their substantial cytotoxicity yields a low SI. (1*R*,1'*S*)-(+)-Homoaromoline (**6**), which presents the same substitution pattern as (+)-limacusine (**5**) and (−)-cycleapeltine (**4**) but with a different absolute configuration, is not as cytotoxic, and this difference is reflected in reduced activity against both clones. *O*-Methylation at C-7' of (+)-homoaromoline (**6**), as in (+)-obaberine (**7**), leads to a slight decrease in cytotoxicity, while the antiplasmodial IC_{50} increases approximately twofold for both clones. No change in activity is observed when the hydroxyl group is at C-6', as in (+)-stephibaberine (**8**), instead of C-7', as in (+)-homoaromoline (**6**). Demethylation at N-2 in (+)-homoaromoline (**6**) to give (1*R*,1'*S*)-(+)-daphnandrine (**9**) does not significantly alter the antiplasmodial activity against the D6 and W2 clones, or the KB cytotoxicity. It is interesting to note that, of the 53 compounds tested so far, this is the

Chart 2



16 : 1*S*, 1'*S*; R_1=Me; R_2=Me

17 : 1*R*, 1'*R*; R_1=Me; R_2=Me

18 : 1*R*, 1'*S*; R_1=Me; R_2=Me

20 : 1*S*, 1'*S*; R_1=H; R_2=Me

21 : 1*R*, 1'*R*; R_1=H; R_2=Me

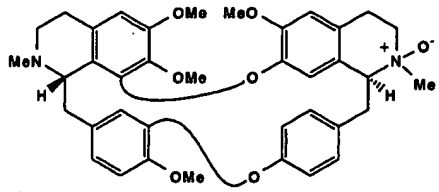
22 : 1*R*, 1'*S*; R_1=H; R_2=Me

23 : 1*R*, 1'*S*; R_1=Me; R_2=H

24 : 1*S*, 1'*S*; R_1=H; R_2=H

25 : 1*R*, 1'*S*; R_1=H; R_2=H

26 : 1*S*, 1'*R*; R_1=H; R_2=H



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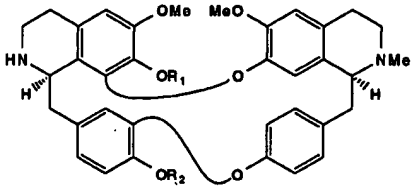
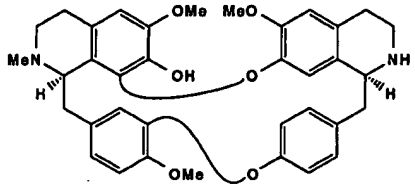
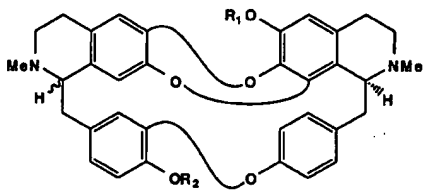


27 : R_1=Me; R_2=H **29** : R_1=H; R_2=Me

28 : R_1=Me; R_2=Me



30



31 : 1*S*; R_1=H; R_2=H **34** : 1*S*; R_1=Me; R_2=H

32: 1*S*; R_1=Me; R_2=H **36** : 1*S*; R_1=Me; R_2=Me

33 : 1*S*; R_1=H; R_2=Me

only case in which no change in bioactivity was found when a hydrogen atom replaced the methyl group at N-2.

The two other 2-nor compounds of this subgroup are (1*R*,1'*S*)-(+)-2-norobaberine (**10**) and (1'*R*,1'*S*)-(+)-2-norcepharanthine (**11**). Both compounds are between twofold and fivefold more active against the W2 and D6 clones than the corresponding *N*-methylated compounds. Despite a slight increase in mammalian cytotoxicity, the alkaloids bearing a secondary amine at N-2 exhibit a slight, but consistent, increase in selectivity.

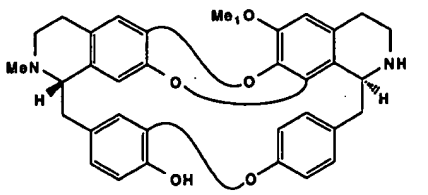
In the group of 12 alkaloids considered thus far, (1*S*,1'*S*)-(−)-repandine (**13**) is the most interesting, with an SI of 350 for the D6 clone and 220 for the W2 clone. (1*R*,1'*R*)-(+)-Candicusine (**14**) displays antiplasmodial IC_{50} values similar to (+)-repandine (**13**), but increased cytotoxicity results in lower selectivity. The *O*-methylation of (+)-candicusine (**14**) at C-12 leads to (1*R*,1'*R*)-(+)-limacusine (**5**). This change of substitution increases the toxicity and decreases the antiplasmodial activity for both clones by about twofold; thus, a fourfold loss in selectivity is observed for (+)-limacusine (**5**). The change of configuration at C-1' in (1*R*,1'*R*)-(+)-candicusine (**14**), as in (1*R*,1'*S*)-(+)-aromoline (**15**), leads to a slight decrease in the cytotoxicity, but activity against *P. falciparum* diminishes more than tenfold.

Fifteen of the bisbenzylisoquinoline alkaloids tested possess an 8,7'/11,12' linkage. (1*S*,1'*S*)-(+)-Tetrandrine (**16**), (1*R*,1'*R*)-(−)-phaeanthine (**17**), (1*R*,1'*S*)-(+)-isotetrandrine (**18**), and (1*R*,1'*S*)-(+)-tetrandrine 2'-β-*N*-oxide (**19**) present the same substitution pattern with four methoxyl groups at C-6, C-7, C-6', and C-12 (Chart 2). (+)-Tetrandrine (**16**) is two times more cytotoxic than (−)-phaeanthine (**17**) and (+)-isotetrandrine (**18**), while activity against the D6 clone is very similar for these three bisbenzylisoquinoline alkaloids. Against the W2 clone, (+)-isotetrandrine (**18**) is six times more active than (−)-phaeanthine (**17**) and four times more active than (+)-tetrandine (**16**). The presence of an *N*-oxide function at N-2 dramatically decreases the cytotoxicity as well as the antiplasmodial activity.

(1*S*,1'*S*)-(+)-Fangchinoline (**20**), (1*R*,1'*R*)-(−)-limacine (**21**), and (1*R*,1'*S*)-(+)-thalrugosine (**22**) bear a hydroxyl at C-7, while C-6, C-6', and C-12 are substituted by a methoxyl group. As observed for (1*S*,1'*S*)-(+)-tetrandrine (**16**), (+)-fangchinoline (**20**), also having the (1*S*,1'*S*)-configuration, is the most cytotoxic. (−)-Limacine (**21**), the mirror image of (+)-fangchinoline, is less toxic and about twice as active as the two other alkaloids against the D6 clone. This difference leads to a better SI for (−)-limacine (**21**) against the D6 clone. The demethylation of (+)-isotetrandrine (**18**) at C-12, as seen in (1*R*,1'*S*)-(+)-berbamine (**23**), tends to increase the toxicity against the D6 clone, but decreases activity against W2 almost fourfold.

(1*S*,1'*S*)-(+)-Atherospermoline (**24**), (1*R*,1'*S*)-(+)-obamegine (**25**), and (1*S*,1'*R*)-(−)-*N*-methyl-7-*O*-demethylpeinamine (**26**) differ in configuration but have the same general substitution pattern (methoxyl groups at C-6 and C-6' and hydroxyl groups at C-7 and C-12). The change of configuration at C-1' from 1'*S* to 1'*R* or the change of configuration from 1*S* to 1*R* leads to a notable decrease in cytotoxicity (3−4-fold), while the effect on antiplasmodial

Chart 3



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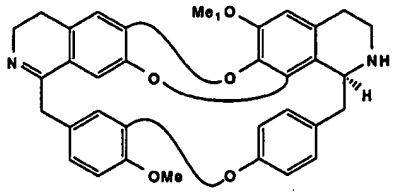

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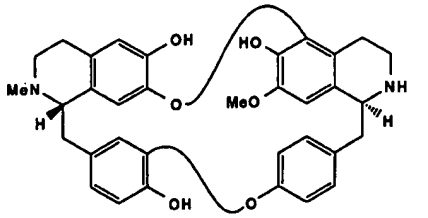
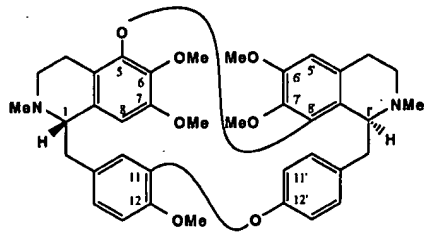


38



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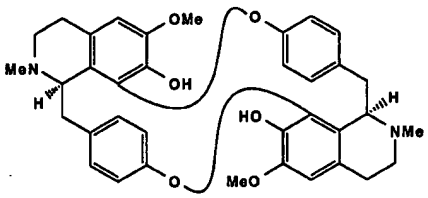

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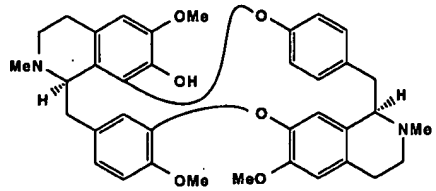


41

IC_{50} values is minor and inconclusive. None of these compounds shows impressive selectivity against *P. falciparum*.

The demethylation of N-2 in (+)-berbamine to yield **27**, in (+)-isotetrandrine to yield **28**, and in (+)-thalrugosine to yield **29** does not affect cytotoxicity, although the antiplasmodial IC_{50} values showed a consistent decrease. In contrast, the demethylation of N-2′, as in 2′-*N*-norlimacine (**30**), increases cytotoxicity by more than fivefold, while antiplasmodial activity is almost unchanged.

Seven of the test compounds represent the bisbenzylisoquinoline subgroup containing three etheroxy bridges. (1*S*,1′*S*)-(+)-Tricordatine (**31**), (1*S*,1′*S*)-(+)-isotrilobine (**32**), (1*S*,1′*S*)-(+)-12-*O*-methyltricordatine (**33**), and (1*S*,1′*S*)-(+)-cocsuline (**34**) differ only in the nature of the substituents at C-12 and C-6′. When the two hydroxyl groups of (+)-tricordatine (**31**) are methylated, as in (+)-isotrilobine (**32**), the cytotoxicity decreases by approximately fourfold, with a proportionate decrease in antiplasmodial activity. The consequence is that the SI is in the same range for both alkaloids.

If only one of the hydroxyl groups is methylated, as in (+)-12-*O*-methyltricordatine (**33**) and (+)-cocsuline (**34**), the cytotoxicity is intermediate between the toxicity of (+)-isotrilobine (**32**) and of (+)-tricordatine (**31**). When only C-6′ bears a methoxyl group as in (+)-cocsuline (**34**), the activity against KB and W2 decreases compared to that of (+)-tricordatine (**31**), although activity against the D6 clone appears unchanged. In the case of a methoxyl at C-12, that is, (+)-12-*O*-methyltricordatine (**33**), the toxicity is similar to that observed for (+)-tricordatine (**31**); however, the antiplasmodial activity is increased more than twofold against both clones of *Plasmodium*. Comparing the activities of (+)-cocsuline (**34**) and (+)-2′-norcocsuline (**35**, Chart 3), it may be noted that the replacement of a methyl group at N-2′ by a hydrogen atom leads to a twofold increase in cytotoxicity, which is paralleled by a twofold increase in antiplasmodial activity, which results in SIs that are essentially unchanged.

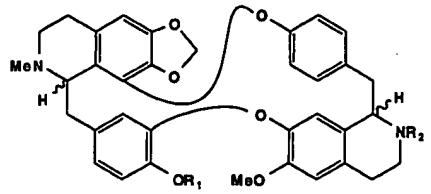
In the same manner, the observed increase in the antiplasmodial activity from (1*S*,1′*S*)-(+)-isotrilobine (**32**) and (1*R*,1′*S*)-(+)-*N*-methyltelobine (**36**), respectively, correlated with an increase in cytotoxicity, and this may be related to the change of configuration at C-1. Oxidation of the secondary amine at N-2′, as in (1′*S*)-(+)-1,2-dehydrotelobine (**37**), decreased the activity against the D6 clone, while the cytotoxicity increased, thereby reducing the SI.

(1*S*,1′*S*)-(−)-6,12-*O*-Demethylthalmine (**38**) is the only representative of its subgroup with a C-7,C-5′ and a C-11,C-12′ linkage. Due to the relatively high IC_{50} values observed with both clones of *Plasmodium* and appreciable cytotoxicity, it did not yield a promising SI.

(1*S*,1′*S*)-(+)Thalmirabine (**39**) belongs to a rare subgroup of bisbenzylisoquinoline alkaloids possessing two etheroxy bridges at C-8,C-5′ and C-11,C-12′. IC_{50} values against both clones of *Plasmodium* indicate good antiplasmodial activity, but the high cytotoxicity results in only modest selectivity.

The remaining compounds, summarized in Table 1, are head-to-tail dimers and belong to three different groups. (1*R*,1′*R*)-(−)-Cycleanine (**40**) was the only available compound representing its subgroup (two etheroxy bridges at C-8,C-12′ and C-12,C-8′). It is important to note that the substitution pattern is identical in each benzylisoquinoline moiety, and the same configuration at C-1 and C-1′ lends

Chart 4



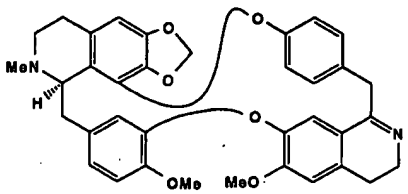
42 : 1*R*, 1'*S*; R_1=Me R_2=H

43 : 1*R*, 1'*R*; R_1=Me; R_2=H

44 : 1*S* 1'*R*; R_1=Me; R_2=COMe

45 : 1*R* 1'*R*; R_1=H; R_2=COMe

46 : 1*R* 1'*R*; R_1=Me; R_2=COMe



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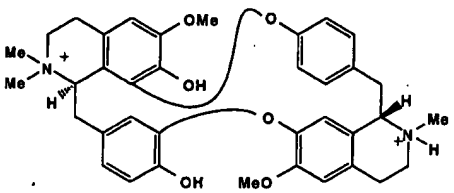
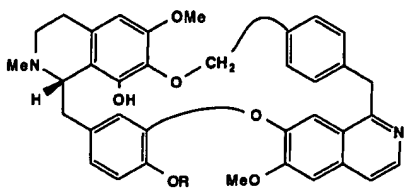
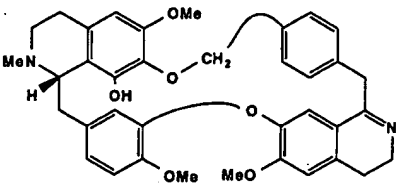


48

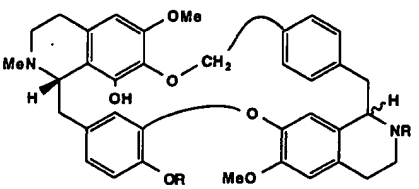


49 : R=Me

50 : R=H



51



52 : R=H

53: R=COMe

a perfect symmetry to the molecule, which is reflected in the ^{1}H NMR spectrum.[2] It is therefore a true dimer. As with (+)-temuconine (**2**), the lack of cytotoxicity observed with (+)-cycleanine (**40**) is remarkable among the bisbenzylisoquinoline alkaloids tested to date. Moreover, relatively potent antiplasmodial activity was observed, leading to impressive SIs of >460 against D6 and >140 against the W2 clone.

Eight of the bisbenzylisoquinoline alkaloids evaluated belonged to the (−)-curine (**41**) group with two etheroxy bridges at C-8, C12′ and C-11,C-7′. None of these eight alkaloids showed appreciable antiplasmodial selectivity. The 2′-*N*-acetylation seen in (−)-curicycleatjenine (**44**), (−)-isocuricycleatjine (**45**), and (−)-isocuricycleatjenine (**46**) greatly decreased their activity against both *P. falciparum* clones, while the cytotoxicity was unchanged or slightly lower. The presence of two quaternary nitrogen atoms, as in (−)-tubocurarine (**48**), leads to a lack of toxicity against KB cells, and of activity against both *Plasmodium* clones. (Chart 4).

The last five compounds tested belong to a subgroup of bisbenzylisoquinoline alkaloids that, thus far, have been isolated only from *Cyclea atjehensis*. The two benzylisoquinoline moieties are linked by an etheroxy bridge at C-11,C-7′ and by a methylenoxy bridge at C-7,C-12′. (+)-Cycleatjehenine (**49**) and (+)-cycleatjehine (**50**) possess a pyridine ring. (+)-Cycleatjehenine (**49**) exhibits an ED_{50} against KB cells of 14 700 nM, with a much lower IC_{50} against both clones of *Plasmodium*. The result is an SI of >100. Demethylation at C-12, as in (+)-cycleatjehine (**50**), does not interfere with the antiplasmodial activity, but decreases KB cytotoxicity twofold, thereby increasing the selectivity. The partial reduction of the pyridine ring, as in 1′,2′-dihydrocycleatjehenine (**51**), does not obviously alter the cytotoxicity (limited by the screening concentration used for the assay) but decreases the antiplasmodial activity threefold. When ring B′ is further reduced, as in (+)-2′-noratjecycline (**52**), no change is observed in the antiplasmodial activity, but the cytotoxicity increases about fourfold. The presence of a 2′-*N*-acetyl group (**53**) gives slightly lower toxicity and an approximately threefold decrease of the antiplasmodial activity.

Within each subgroup of bisbenzylisoquinolines analyzed, we have shown that a change of configuration of the chiral center, as well as modification of substituents, may lead to independent changes in cytotoxicity and antiplasmodial activity. However, except for the three one-bridged compounds, (+)-neothalibrine (**1**), (+)-temuconine (**2**), and (+)-malekulatine (**3**), which show low toxicity and appreciable antiplasmodial activity, the current results do not reveal any clear structure−activity relationship between subgroups of bisbenzylisoquinoline alkaloids. With the

exception of the one-bridged bisbenzylisoquinolines, all possess a large heterocycle of 18 to 20 atoms, which confers flexibility to the molecule. A study of the conformations assumed by compounds of the same subgroup (i.e., modification of conformation with the change of configuration at C-1 and C-1′) should give more information about the structure–activity relationship.

Within the limits of our data, several remarks may be made. The quaternarization of one or two nitrogen atoms, as in compound **48**, leads to a loss of toxicity and antimalarial activity. The same effect is observed by *N*-oxide formation in compound **19**. The presence of an acetyl function at N-2′, as in compounds **44**, **45**, **46**, and **53**, also results in a decrease in the cytotoxicity and antimalarial activity observed. The decrease in lipophilicity (membrane permeability) of all of these alkaloids probably contributes to the lower toxicity observed.

Nonetheless, it must be stressed that this group of natural compounds exhibits selective toxicity toward cultured malarial parasites. In terms of SI, some compounds compare favorably with known antimalarial agents (Table 1). Based on these data, it may be suggested that certain bisbenzylisoquinolines are worth considering as potential antimalarial agents. In this endeavor, the most promising compounds will need to be tested with in vivo models to define more clearly the structure–activity relationships and true efficacy. Compounds with favorable SI values represent reasonable starting materials, but based on resulting in vivo data, the compounds could be synthetically modified to yield drugs with higher selectivity. These studies may also provide valuable insight into new mechanisms of antiplasmodial action or structure–activity relationships.

Experimental Section

All compounds have been isolated by the authors or their research groups as referenced above. Immediately prior to biological testing, all compounds were purified by preparative TLC on Si gel. Greater than 95% purity, as verified by ^{1}H NMR spectroscopy, was considered acceptable.

Plasmodial Culture System. Cultures of *Plasmodium falciparum* (chloroquine-sensitive clone D6 derived from CDC Sierra Leone, and chloroquine-resistant clone W2 derived from CDC Indochina III) were maintained in human erythrocytes according to established methods.[18] Parasites were inoculated into type A+ human erythrocytes at a hematocrit of 6% in RPMI-1640 culture medium (GIBCO Laboratories, Grand Island, NY) supplemented with 32 mM $NaHCO_3$ (GIBCO), 25 mmol HEPES (*N*-2-hydroxyethylpiperazine-*N*-2-ethanesulfonic acid, Sigma Chemical Co., St. Louis, MO), and 10% heat-inactivated human plasma type A+. Parasitemia was maintained below 4% under an atmosphere of 5% O_2, 5% CO_2, and 90% N_2 in 25 cm^2 culture flasks at 37 °C.

Antiplasmodial Bioassay. The antiplasmodial activity of test compounds was assessed with an in vitro radioisotope-incorporation method.[19] A suspension (200 μL) of *P. falciparum*-infected red blood cells (0.5–1.0% parasitemia, 1.0% cell hematocrit) was added to wells of a standard 96-well tissue culture plate containing 25 μL of substance to be tested. Each test compound was assayed in duplicate over a seven-point concentration range. In addition, the known antimalarial drugs quinine, chloroquine, mefloquine, and artemisinin were tested in each experiment over a seven-point concentration range. Microtiter plates were incubated for 24 h at 37 °C in a sealed chamber under an atmosphere of 5% CO_2, 5% O_2, and 90% N_2. After this incubation period, 0.5 μCi of ^{3}H(G)-hypoxanthine (New England Nuclear Research Products, Boston, MA, NET 177) was added to each well (25 μL of 20 μCi/mL), and the microtiter plate was returned to the sealed chamber at 37 °C for an additional 18 h of incubation. The assay was terminated by harvesting the contents of each microtiter plate onto a glass fiber filter using a Tomtec Mach III automatic cell harvester. Filters were dried and placed in polyethylene bags with 3.5 mL of biologically safe scintillation cocktail. Radioactivity was determined with a Wallac Microbeta liquid scintillation counter. Concentrations of both test compounds and positive controls that inhibited parasite-specific incorporation of [^{3}H]hypoxanthine by 50% (IC_{50}) were determined by nonlinear regression analysis. Zero-drug controls defined 100% incorporation. Limitations of the radioisotope-incorporation protocol include the acknowledgment that some antimalarials acting at the vector or exoerythrocytic stages of the life cycle or as gametocidal agents may be missed by an assay that depends on erythrocytic schizogony. Other limitations of this assay include the reliance upon some undefined media: the blood cells are obtained from different human donors at frequent intervals and thus introduce a degree of unavoidable variability. This was compensated for by including the IC_{50} data of the known antimalarial standard drugs with the report of each assay (mean ± standard error is shown in Table 1 for all standard drugs). Sample data were rejected unless the chloroquine-sensitive, quinine-sensitive, mefloquine-resistant phenotype of clone D6 and the chloroquine-resistant, quinine-resistant, mefloquine-sensitive phenotype of clone W2 showed appropriate responses.

Cytotoxicity Screening and ED_{50} Determination. KB-3 cells were cultured in Dulbecco's Modified Eagle's Medium (GIBCO) supplemented with 10% fetal bovine serum (Atlanta Biologicals) and penicillin–streptomycin–fungizone (GIBCO) at 37 °C at 100% relative humidity with 5% CO_2 in air.

Evaluation of Cytotoxic Potential.[5,17] Cells were typically grown to 60%–70% confluence; the medium was then changed, and the cells were used for test procedures 1 day later. In each case, 96-well tissue culture plates were used. Test samples were initially dissolved in DMSO, and then diluted tenfold with H_2O. Serial dilutions were then performed using 10% aqueous DMSO as the solvent; 5×10^4 cells (in 190 mL of media) were then added to the 96-well plates and incubations performed for 72 h. All incubations were performed at 37 °C in a CO_2 incubator with the plates covered by vented plastic lids.

After the incubation period, cells were fixed to the plastic substratum by the addition of 50 μL of cold 50% aqueous trichloroacetic acid. The trichloroacetic acid-fixed cells were then stained by the addition of 0.4% sulforhodamine B (w/v) dissolved in 1% HOAc (30 min) and washed with 1% aqueous HOAc (4 ×). The bound dye was solubilized by the addition of 10 mmol unbuffered Tris base, pH 10 (200 μL). The absorption was determined at 515 nm using an ELISA plate reader. In each case, a zero-day control was performed by adding an equivalent number of cells to several wells of the 96-well plates and incubating at 37 °C for 10 min. The cells were then fixed with trichloroacetic acid and processed as described above.

Finally, the absorption values obtained with each of the treatment procedures were averaged, and the average value obtained with the zero-day control was subtracted. These values were then expressed as a percentage, relative to the solvent-treated control incubations, and ED_{50} values were calculated using nonlinear regression analysis (percent survival versus concentration). These experimental conditions were established in preliminary studies wherein it was shown (a) there is at least a sevenfold increase in cell number relative to the number of cells added to the plates at time zero; (b) the resulting absorption values are in an appropriate range to ensure reading accuracy (i.e., > 1.4 A_{515} units); and (c) the cell number attained during the incubation period did not reach a plateau region on the growth curve.

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References and Notes

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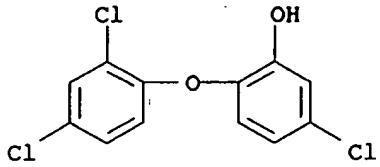
NP980144F

IT **3380-34-5**, 2,4,4'-Trichloro-2'-hydroxydiphenyl ether
RL: MOA (Modifier or additive use); USES (Uses)
(Antimicrobials; antimicrobial radiation curable acrylic urethane polymer coating)
RN 3380-34-5 HCAPLUS
CN Phenol, 5-chloro-2-(2,4-dichlorophenoxy)- (7CI, 8CI, 9CI) (CA INDEX NAME)



IT **70-30-4**, Hexachlorophene
RL: MOA (Modifier or additive use); USES (Uses)
(antimicrobials; antimicrobial radiation curable acrylic urethane polymer coating)
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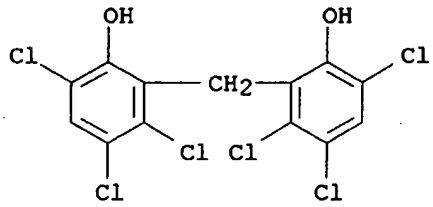
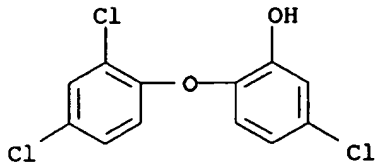


L7 ANSWER 3000 OF 5877 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1984:401909 HCAPLUS
DOCUMENT NUMBER: 101:1909
TITLE: The acute toxicity of penta-, hexa-, and heptachlorohydroxydiphenyl ethers in mice
AUTHOR(S): Miller, Terry L.; Lorusso, David J.; Walsh, Marilyn L.; Deinzer, Max L.
CORPORATE SOURCE: Dep. Agric. Chem., Oregon State Univ., Corvallis, OR, 97331, USA
SOURCE: Journal of Toxicology and Environmental Health (1983), 12(2-3), 245-53
CODEN: JTEHD6; ISSN: 0098-4108
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The acute i.p. LD50s for chlorinated hydroxydiphenyl ethers (I, n = 5-7) in mice were detd. The acute toxicities were on the order of, or slightly less than, that detd. previously for 2-hydroxy-2',4,4'-trichlorodiphenyl ether (II) [**3380-34-5**]. However, the acute toxicities detd. for I were substantially less than those detd. for the perchlorohydroxydiphenyl ethers and pentachlorophenol [87-86-5]. I had a marked hypothermic effect, similar to II. Symptomatol. following exposure

to I suggested a nonspecific depressant effect on the central nervous system.

IT **3380-34-5 53555-01-4 61639-90-5**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (toxicity of)

RN 3380-34-5 HCAPLUS
CN Phenol, 5-chloro-2-(2,4-dichlorophenoxy)- (7CI, 8CI, 9CI) (CA INDEX NAME)



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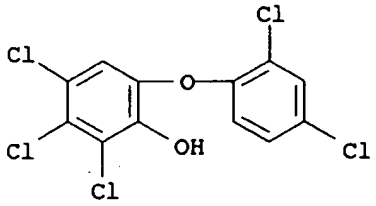
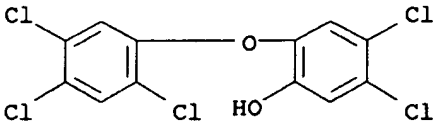


RN 61639-90-5 HCAPLUS
CN Phenol, 4,5-dichloro-2-(2,4,5-trichlorophenoxy)- (9CI) (CA INDEX NAME)



L7 ANSWER 3001 OF 5877 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1984:211977 HCAPLUS
DOCUMENT NUMBER: 100:211977
TITLE: Caustic-sensitive, water-resistant labeling adhesive
INVENTOR(S): Jannusch, Leonard C.
PATENT ASSIGNEE(S): Fuller, H. B., Co., USA
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

Evaluation of the Anti-Plasmodial Activity of Bisbenzylisoquinoline Alkaloids from *Abuta grandifolia*

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Revision accepted: February 7, 1999; Received: October 23, 1998

Abstract: Three alkaloids were isolated from the bark of the traditional medicinal plant *Abuta grandifolia* (Mart.) Sandw. (Menispermaceae) and tested for *in vitro* anti-plasmodial activity. Two of them were identified as the Type VIII bisbenzylisoquinoline alkaloids, krukovine (**1**) and limacine (**2**), while the least abundant compound (**3**) could only be characterised to Type I of the same class. Krukovine exhibited potent anti-plasmodial activity with IC_{50} values of 0.44 μg/ml and 0.022 μg/ml against K1 (chloroquine-resistant) and T9-96 (chloroquine-sensitive) *Plasmodium falciparum*, respectively. Both limacine and compound **3** exhibited moderate anti-plasmodial activity against K1 with IC_{50} values of 1.35 μg/ml and 1.58 μg/ml, respectively. Limacine gave an IC_{50} value of 0.24 μg/ml against T9-96. Krukovine and limacine showed greater activity against T9-96 than against K1, exhibiting similar activity profiles to that of chloroquine diphosphate (0.187 μg/ml and 0.013 μg/ml against K1 and T9-96, respectively). This indicates that krukovine and limacine may be affected by the mechanism of chloroquine resistance present in K1 *P. falciparum*.

Key words: *Abuta grandifolia*, Menispermaceae, bisbenzylisoquinoline alkaloids, anti-malarial, anti-plasmodial, *Plasmodium falciparum*.

Introduction

The deterioration in the efficacy of conventional anti-malarial drugs is a matter of great concern. At present there are no drugs than can offer protection against malaria in all regions of the world, and the need for novel chemotherapeutic agents is therefore acute. Plants are a potential source of new anti-plasmodial compounds and are therefore the focus of much current interest (1). At present the most effective anti-malarial leads appear to be derived from plants used traditionally to treat malaria, such as artemisinin from *Artemisia annua* (Compositeae) (2). *Abuta grandifolia* has been selected as part of a study to evaluate the plants used in South America as traditional medicines. An infusion of the inner trunk bark of this species is used in South America for the treatment of malaria (3). In this paper we report the isolation of three bisbenzylisoquinoline alkaloids from *A. grandifolia* and the evaluation of their anti-plasmodial activity against chloroquine resistant and sensitive *P. falciparum*.

Materials and Methods

Instrumentation

HPLC was carried out using a Waters 600E controller, 717 Plus autosampler, 60F pump module and a 996 photodiode-array detector. A Waters Radial-Pak Nova-Pak C_{18} column (100 × 8 mm i.d., 4 μm) was used for both analytical and semi-preparative work. The elution programme was based on a method described previously (4), with gradient elution over 40 minutes at 2 ml/min from 80:20 to 60:40 A:B where A was 0.2 ml 60% $HClO_4$ (BDH) per 1 L 0.15 M $NaClO_4$ (BDH) in water and B was pure acetonitrile (Fisher). UV-VIS spectra were recorded on a Shimadzu UV-1601 spectrophotometer. MS were determined by direct injection using a ThermoQuest Corp. LCQ quadrupole ion-trap with an APCI interface in positive ion mode. ^1H- and ^{13}C-NMR spectra were obtained on either a Varian 500 MHz or a Jeol 270 MHz spectrometer. Specific optical rotation was determined using an AA-5 Polarimeter (Optical Activity Ltd.), at 20.0 °C.

Plant material and nomenclature

Trunk bark of *A. grandifolia* (Mart.) Sandw. was collected by Mr. William Milliken from the Roraima State of Northern Brazil and authenticated at the Royal Botanic Gardens, Kew, U.K. A voucher specimen has been deposited in the Herbarium, Royal Botanic Gardens, Kew (No. Milliken-1956). It should be noted that several species have been described previously as *A. grandifolia* (Mart.) Sandw. Those reclassified as *A. grandifolia* (Mart.) Sandw. include *A. concolor* Poepp & Endl. together with *A. concolor* Benth (5) and *Cocculus grandifolius* (6). *A. concolor* Benth was previously classified as *A. guianensis* Eichl. (7).

Extraction and isolation procedures

Soxhlet extraction of 60 g powdered bark of *A. grandifolia* with 90% MeOH for 20 h yielded an oily brown residue (12.7 g) after evaporation. 30 mg of this material were retained for bioassay, and the remainder suspended in 600 ml 0.5 M HCl

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overnight, filtered into a separating funnel and the filtrate partitioned with $CHCl_3$ (2 × 600 ml). The organic layers were combined and concentrated to yield fraction A (151 mg). The aqueous layer was made alkaline by addition of NH_4OH to pH 12 and re-partitioned with 3 × 600 ml $CHCl_3$. These partitions were combined and concentrated to yield fraction B (730 mg). Fractions A and B were both tested for anti-plasmodial activity. Fraction B was subjected to VLC fractionation over silica gel (4 × 4 cm column) using step gradient elution (30 ml volumes of $CHCl_3$: MeOH: 6 × 100 : 0, 12 × 95 : 5, 12 × 90 : 10, 8 × 80 : 20, 8 × 60 : 40, 2 × 0 : 100). The resulting fractions were combined according to their TLC profiles on analytical silica plates (Merck) using $CHCl_3$: MeOH : NH_3 (89 : 10 : 1), as detected by UV and Dragendorff reagent, to give fractions B1 to B8. Fraction B5 (VLC fractions 21 – 24) was fractionated by column chromatography (Lobar 310 × 25 mm, Merck) over silica gel employing isocratic elution with diethylamine (DEA) : EtOAc (5 : 95) at a flow rate of 4 ml/min. The compound which eluted between 470 and 660 ml recrystallised from $CHCl_3$ to yield 38 mg of **1**. Fractions B4 (VLC fractions 16 – 20) and B8 (VLC fractions 36 – 48) were further fractionated by preparative TLC over silica gel; B4 was eluted twice with DEA : toluene (10 : 90) to yield fraction B4.1 (R_f 0.49 – 0.58) and B8 eluted four times with DEA : MeOH : toluene (1 : 1 : 8) to yield fraction B8.1 (R_f 0.35 – 0.4). Further purification by HPLC of fractions B4.1 and B8.1 yielded 4.1 mg of **2** (t_R 25.0 min) and 2.8 mg of **3** (t_R 14.7 min), respectively, the free bases being back-extracted from the HPLC eluate into $CHCl_3$ under alkaline conditions.

Physical properties

Krukovine (**1**): White crystals from chloroform. UV: λ_{max} = 209, 235sh, 285 nm. APCI-MS, positive mode: *m/z* = 595 $[M + 1]^+$. $[\alpha]_D$: – 184°, (*c* 0.06, $CHCl_3$). ^{1}H-NMR (500 MHz, d_6-DMSO, 37 °C): δ = 2.17 (3H, s, 2-NCH_3), 2.30 and 2.58 (2 × 1H, 2 × m, H-α), 2.32 and 2.79 (2 × 1H, 2 × m, H-4), 2.54 (3H, s, 2′-NCH_3), 2.74 and 3.19 (2 × 1H, 2 × m, H-α′), 2.76 and 3.39 (2 × 1H, 2 × m, H-3), 2.77 and 2.80 (2 × 1H, 2 × m, H-4′), 2.77 and 3.26 (2 × 1H, 2 × m, H-3′), 3.25 (3H, s, 6′-OCH_3), 3.52 (1H, d, *J* = 9.5 Hz, H-1), 3.66 (3H, s, 6-OCH_3), 3.90 (1H, dd, *J* = 5.6, 10.4 Hz, H-1′), 5.90 (1H, s, H-8′), 6.34 (2 × 1H, s, H-5 and H-10), 6.36 (1H, dd, *J* = 2.0, 8.2 Hz, H-10′), 6.58 (1H, s, H-5′), 6.65 (1H, dd, *J* = 1.7, 8.1 Hz, H-14), 6.68 (1H, dd, *J* = 2.0, 8.2 Hz, H-11′), 6.72 (1H, d, *J* = 8.1 Hz, H-13), 7.10 (1H, dd, *J* = 2.0, 8.2 Hz, H-13′), 7.44 (1H, dd, *J* = 2.0, 8.2 Hz, H-14′), 7.69 (1H, br s, 7-OH), 8.96 (1H, br s, 12-OH); ^{13}C-NMR (67.8 MHz, d_6-DMSO, 37 °C); δ = 21.2 (C-4), 25.5 (C-4′), 35.8 (C-α′), 41.5 (C-α), 42.1 (2-NCH_3), 42.2 (2′-NCH_3), 43.6 (C-3), 45.0 (C-3′), 55.9 (6-OCH_3), 56.0 (6′-OCH_3), 61.2 (C-1), 62.7 (C-1′), 105.8 (C-5), 113.2 (C-5′), 115.6 (C-10 and C-13), 119.6 (C-8′), 121.2 (C-11′), 121.4 (C-13′), 122.2 (C-8a), 122.8 (C-4a), 123.0 (C-14), 127.8 (C-4′a), 128.6 (C-8′a), 130.3 (C-14′), 132.4 (C-10′), 132.8 (C-9), 135.1 (C-7), 135.2 (C-9′), 142.4 (C-8), 143.5 (C-7′), 144.2 (C-12), 146.5 (C-6), 147.8 (C-11), 148.0 (C-6′), 153.2 (C-12′).

Limacine (**2**): Amorphous yellow solid from chloroform. UV: λ_{max} = 207, 235sh, 281 nm. APCI-MS, positive mode: *m/z* = 609 $[M + 1]^+$: $[\alpha]_D$: – 205°, (*c* 0.28, $CHCl_3$). ^{1}H- and ^{13}C-NMR spectra identical to those reported previously for limacine (8).

Compound **3**: Amorphous yellow solid from chloroform. UV: λ_{max} = 207, 235sh, 284 nm. APCI-MS, positive mode: *m/z* = 597 $[M + 1]^+$. $[\alpha]_D$: – 15°, (*c* 0.2, $CHCl_3$). ^{1}H-NMR (270 MHz, d_6-DMSO, 37 °C): δ = 2.33 and 2.35 (2 × 3H, 2 × s, 2 × NCH_3), 3.69 and 3.72 (2 × 3H, 2 × s, 2 × OCH_3), 6.34, 6.48, 6.54 and 6.58 (4 × 1H, 4 × s, H-5, H-8, H-5′ and H-8′), 6.65 (2H, d, *J* = 8.1 Hz, H-11′ and H-13′), 6.66 (1H, br s, H-10), 6.77 (2H, br s, H-13 and H-14), 7.05 (2H, d, *J* = 8.1 Hz, H-10′ and H-14′), 8.49 (2H, br s, 2 × OH), 9.05 (1H, br s, OH).

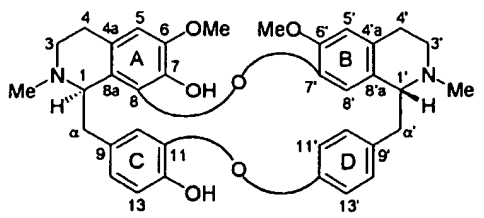
In vitro *anti-plasmodial evaluation*

In vitro cultures of *P. falciparum* [chloroquine- and pyrimethamine-resistant K1 strain from Thailand (9) and the chloroquine-sensitive T9-96 clone (10)] were used for the evaluation of anti-plasmodial activity. Cultures with a very high prevalence of young ring stages (> 95%) were used for the drug tests. Stock solutions of the samples were prepared in DMSO at 8 mg/ml then diluted to the required concentration with complete medium (final DMSO concentrations of < 0.5% exhibited no inhibition of parasite growth). The remainder of the ^{3}*H*-hypoxanthine incorporation assay procedure was as described previously (11) with a final inoculum of 2.5% haematocrit at 1% parasiteamia. Each sample was tested in triplicate. Calculation of IC_{50} values was performed using Excel 5 (Microsoft Corp.) with XL Fit (V. 1.02) "add-in" (ID Business Solutions Ltd, UK).

Results and Discussion

Repetitive chromatography of the alkaloidal fraction from the methanolic extract of *A. grandifolia* trunk bark gave three bisbenzylisoquinoline alkaloids, two of which were identified as krukovine (**1**) (0.06% w/w) and limacine (**2**) (0.007% w/w). The major compound, **1**, was only sparingly soluble in $CDCl_3$ and consequently ^{1}H- and ^{13}C-NMR spectra were obtained in d_6-DMSO. A molecular structure for **1** was obtained using standard DEPT, COSY, HSQC and HMBC experiments. The positions of the hydroxy, methoxy and ether bridge linkages were confirmed using HMBC data. These spectra included useful long-range correlations from the exchangeable hydroxy protons which were retained in d_6-DMSO. An empirical formula of $C_{36}H_{38}N_2O_6$ deduced from the NMR data was consistent with an $[M + 1]^+$ ion of *m/z* 595 obtained by APCI-MS operating in the positive mode. This identified the compound as one of the four possible stereoisomers of the bisbenzylisoquinoline alkaloid, 6,6′-dimethoxy-2,2′-dimethylberbaman-7,12-diol. Comparison of the $[\alpha]_D$ value of – 184° (*c* 0.06, $CHCl_3$) obtained for **1** with optical rotation data for the four stereoisomers confirmed it to be the (1*R*,1′*R*) *anti* stereoisomer known as krukovine, for which an $[\alpha]_D$ value of – 180° has been reported under the same solution conditions (*c* 0.06, $CHCl_3$) (15). Krukovine has been isolated previously from *A. splendida* Krukoff & Moldenke, *Curarea candicans* (L. C. Rich) Barneby & Krukoff and *Pycnarrhena longifolia* Becc. (12), (13), (15), which are all taxa in Menispermaceae. A complete set of ^{1}H- and ^{13}C-NMR resonance assignments for krukovine in d_6-DMSO is given here for the first time, although incomplete sets of ^{1}H-NMR data acquired in $CDCl_3$ have been reported previously (14), (15). (see Fig. **1**).

Compound **2**, which dissolved readily in $CDCl_3$, exhibited identical ^{1}H- and ^{13}C-NMR spectra to those reported for the bisbenzylisoquinoline alkaloid limacine (12-methoxykrukovine) in $CDCl_3$ (8). The $[\alpha]_D$ value of – 205° (*c* 0.28, $CHCl_3$) ob-



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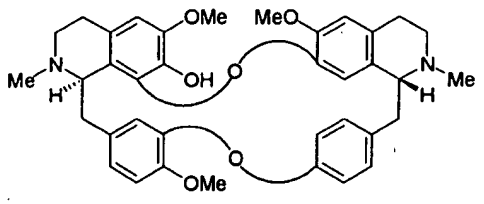

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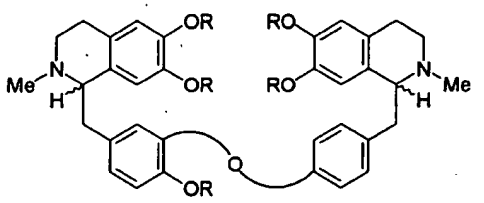

3

Fig. 1

tained for **2** was in good agreement with the literature value of −212° ($CHCl_3$) and confirmed the stereochemistry as (1*R*,1′*R*) (15). Limacine appears to be more widely distributed than krukovine, and occurs in *Gyrocarpus americanus* Jacq. (Hernandiaceae) and several genera of Menispermaceae (12), (13), (15–17). It has not been reported previously in *Abuta* spp, although its occurrence together with krukovine in *A. splendida* is not unexpected.

Compound **3** gave an $[M + 1]^+$ ion of *m/z* 597 in APCI-MS, corresponding to an empirical formula of $C_{36}H_{40}N_2O_6$. The ^{1}H-NMR spectrum obtained for compound **3** in d_6-DMSO, with the distinctive feature of near-coincident *N*-methyl (2.33 and 2.35 ppm) and methoxy (3.69 and 3.72 ppm) proton resonances, was typical of that found for "tail to tail" bisbenzylisoquinoline alkaloids with only a single diaryl ether bridge (from C-11 to C-12′) (14). The aromatic region of the spectrum contained two doublets (2 × 2H, both J = 8.1 Hz) at δ 6.65 and 7.05 ppm, which can be assigned to ring D (H-10′, H-11′, H-13′ and H-14′), and an ABX system at δ 6.66 (1H, br s) and 6.77 (2H, br s) ppm, which can be assigned to ring C (H-10, H-13 and H-14), again supporting the presence of a single diaryl ether bridge in **3**. The remaining aromatic proton resonances at δ 6.34, 6.48, 6.54 and 6.58 ppm (all 1H, s) must originate from rings A and B and can only be accommodated in a 6,7,6′,7′ substitution pattern. The broader exchangeable resonances observed at δ 8.49 (2 × 1H) and 9.05 (1H) ppm, correspond to three hydroxy groups. These data confirm that the substitution pattern of **3** must be 6,7,11 – 12′,12,6′,7′, identifying it as a Type I bisbenzylisoquinoline alkaloid (14). Although the chemical shift values obtained for the *N*-methyl and methoxy proton resonances of **3** are identical to those obtained previously in d_6-DMSO for an alkaloid of this type named grisabutine (also referred to by its original name of magnoline) (15), further data are necessary to afford an unambiguous identification of this minor component of *A. grandifolia*.

In vitro *anti-plasmodial evaluation*

Table **1** shows the *in vitro* anti-plasmodial activity exhibited by the methanol extract, fractions and purified compounds from *A. grandifolia*. The methanol extract had moderate activity, with an IC_{50} of 3.34 μg/ml against the K1 strain, while the alkaloidal fraction B exhibited greater activity (IC_{50} < 0.39 μg/ml) than the acidic partition, fraction A (8.7 μg/ml). The potent activity of krukovine (**1**) together with the moderate activity of limacine (**2**) and compound **3** indicates that these compounds are partly responsible for the activity exhibited by fraction B. The observation that fraction B was more active (97% inhibition at 0.39 μg/ml) than any single compound tested indicates either that the mixture of compounds exerts a synergistic effect or that additional minor compounds with significant activity are present. Krukovine (**1**) was observed to be twenty times more potent against chloroquine-sensitive (T9-96) than against chloroquine-resistant (K1) *P. falciparum*, and thus has an activity profile similar to chloroquine. This suggests that the import or export mechanisms responsible for chloroquine resistance in K1 *P. falciparum* (18), (19) may also affect krukovine (**1**).

Bisbenzylisoquinoline alkaloids have been recently reported to have potent *in vitro* anti-plasmodial activity (8), (20). To our knowledge there is no record of *in vitro* anti-plasmodial activity associated with krukovine (**1**). Limacine (**2**) has been reported to have *in vitro* anti-plasmodial activity (8) but failed to demonstrate *in vivo* anti-malarial activity in mice (*P. berghei*) at 100 mg/kg (16). This alkaloid has also been reported to reverse chloroquine-resistance in *P. falciparum* and vinblastine-resistance in a mammalian cell-line (21). In addition, both krukovine (**1**) and limacine (**2**) have been shown to demonstrate *in vitro* activity against the flagellated protozoa *Leishmania brasiliensis*, *L. amazonensis*, and *L. donovani* (16). In contrast, these compounds exhibited poor activity against *Try-*

Table 1 *In vitro* anti-plasmodial activities of extracts and compounds tested against K1 and T9-96 *P. falciparum*. The ratio of activities K1: T9-96 indicates the extent to which activity is compromised by the K1 chloroquine-resistance mechanism.

Sample tested	K1 IC_{50} μg/ml	T9-96 IC_{50} μg/ml	Ratio K1 : T9-96
Methanol extract	3.34 [0.37]	nt	–
Fraction A	8.73 [0.2]	nt	–
Fraction B	< 0.39 (97%)	nt	–
Krukovine (**1**)	0.44 [0.04]	0.022 [0.002]	20
Limacine (**2**)	1.35 [0.06]	0.24 [0.05]	5.6
Compound **3**	1.58 [0.13]	nt	–
Chloroquine	0.21 [0.001]	0.012 [0.001]	17.5

nt = not tested; Numbers in parentheses are standard errors of the mean (number of replicates = 3).

panosoma cruzi epimastigotes *in vitro*, although limacine (**2**) showed greater efficacy when tested *in vivo* against *Trypanosoma cruzi* infection in mice (16).

In conclusion, the bark of *A. grandifolia* contains bisbenzylisoquinoline alkaloids which show potent anti-plasmodial activity. The results indicate that these compounds could be responsible in part for the anti-malarial activity of this plant. The activity profile of krukovine (**1**), the most potent of the three compounds isolated, suggests that it is subject to the mechanism of chloroquine-resistance in *P. falciparum*, whereas limacine (**2**) has been reported to reverse chloroquine-resistance (21). These compounds may therefore provide a more effective treatment in combination. This may be an important future consideration since the incidence of chloroquine-resistant *P. falciparum* malaria in the Amazon region appears to be on the increase (22).

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W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD				
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AU 9228064	A	19930521	AU 1992-28064	19921013 <--
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